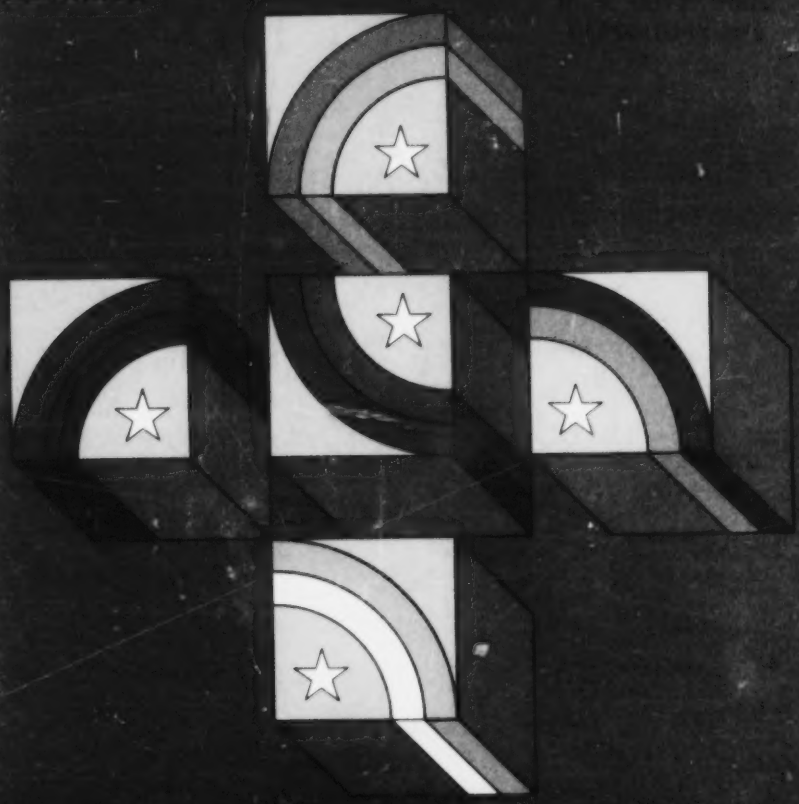
Associate Training Programs in the Medical and Biological Sciences at the National Institutes of Health

1981 Catalog



U.S. DEPARTMENT OF HEALTH AND HUMAN RESOURCES

Public Health Service

National Institutes of Health

1981

February 6	**Deadline for receipt of completed NIH Associate applications**
March 16-27	**Interview period**
April 8-10	**Notification to all candidates**

Applications may be obtained from:

The NIH Associate Program
Building 31, Room 4B04
National Institutes of Health
Bethesda, MD 20205
Tel: 301-496-2427

Discrimination Prohibited: Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the ground of race, color, national origin, sex, or handicap, be excluded from participation in, be denied the benefits of, or be subject to discrimination under any program or activity receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of Federal contracts. Therefore, the NIH Associate Training Program must be operated in compliance with these laws and executive order.

Please note the following changes in the Associate Catalog:

In the National Cancer Institute:
Dr. Vincent T. DeVita is now Director and Clinical Director.

Dr. Bruce A. Chabner is now Acting Associate Director, Clinical Oncology Program, and Acting Deputy Clinical Director, NCI.

In the Clinical Center:
There is currently no residency training program in the Clinical Pathology Department.

Foreword

The National Institutes of Health and the Clinical Center, the research hospital for the Institutes, are international centers for biomedical research and clinical investigation. The Clinical Center and the other intramural research facilities in Bethesda have provided research and training opportunities for thousands of foreign scientists and physicians and for an even greater number of research scientists and clinical investigators in this country.

The Clinical Center has 540 beds to which patients are admitted for participation in research protocols. The protocols are directed towards understanding disease as well as towards diagnosis and treatment. The proximity of the wards to the 1,100 research laboratories ensures continuing collaboration between clinical and laboratory scientists. Within this scientific community there are unique opportunities to acquire the skills necessary for biomedical research. This catalog describes the opportunities open to physicians and dentists in the Associate Program at the NIH.

Mortimer B. Lipsett, M.D.
Director
The Clinical Center

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Part One

General Description of Associateships and Other Opportunities

The Clinical Center

Mortimer B. Lipsett, M.D.,
Director
Griff T. Ross, M.D., Ph.D.
Deputy Director
Jay R. Shapiro, M.D.,
Associate Director

The Clinical Center is a modern laboratory hospital facility shared by the 10 Institutes that conduct combined laboratory and clinical study programs. This 540-bed research hospital is located on a 300-acre campus at the National Institutes of Health (NIH) in Bethesda, Maryland.

NIH is the largest biomedical research organization in the world. Approximately 2,400 staff members have doctoral degrees, including almost 1,000 with M.D. degrees, more than 1,200 with Ph.D. degrees, and about 50 with D.D.S. and 50 with D.V.M. degrees. A significant number have more than one doctorate.

Four Nobel laureates work on the campus: Drs. D. Carleton Gajdusek, Christian B. Anfinsen, Julius Axelrod, and Marshall W. Nirenberg. Dr. Gajdusek received the award in 1976 for his work in proving that kuru—a fatal disease affecting the nervous system—is a transmissible slow virus infection. The prize was given to Dr. Anfinsen in 1972 for his studies of ribonuclease, particularly the relationship between amino acid sequences and the conformation of enzyme molecules.

In 1970, Dr. Axelrod was cited for discoveries concerning transmitter substances in nerve terminals and mechanisms for their storage, release, and deactivation. Dr. Nirenberg was honored in 1968 for his work on the translation of the genetic code and its function in protein synthesis.

Two other scientists received the Nobel prize for work done while at NIH. Dr. Arthur Kornberg received the award in 1959 for his research on the mechanisms in the biological synthesis of DNA and RNA. In 1976, Dr. Baruch Blumberg was honored for his discovery of the "Australia antigen," a marker of hepatitis B.

With the help of a staff of almost 5,000 technical personnel, NIH scientists are involved in some 2,700 research projects which result in more than 4,000 published scientific articles each year. The budget for this intramural research effort is almost $300 million.

The 14-story Clinical Center represents an important resource for training in medical research. The hospital provides a setting in which a young physician can participate in medical care, acquire new clinical skills, and

carry out research in a laboratory conveniently located a few steps from the patient's room. The center is designed to bring scientists working in laboratories into close proximity with clinicians caring for patients so that bench investigators and physicians may collaborate on problem diseases.

The primary mission of the Clinical Center is to provide a specialized form of hospital care necessary for Institute studies. To accomplish this goal, the Clinical Center has developed patient care programs and related technical support systems which stand at the fore of modern health care. Illustrative of this is the surgical wing, a four-story circular structure, which contains one of the most comprehensive and modern monitoring systems in the world.

The Nuclear Medicine Department provides computerized axial tomography, whole-body scanning, and diagnostic imaging through the use of radioactive pharmaceuticals. The department is developing novel diagnostic procedures aimed at resolving certain problems of medical diagnosis through the use of nuclear medicine technology. The Diagnostic Radiology Department has a full complement of radiological equipment, including CAT scanners and ultrasonic scanners. Increasing emphasis in this department is being placed on the development of interventional radiographic techniques. The superbly equipped Clinical Pathology laboratories provide optimum support to physicians and their patients. The Blood Bank provides blood products for the patients, teaches blood banking and immunohematology, and conducts research.

Numerous opportunities are available for associates to participate in the use and development of modern medical computer systems, medical instrumentation and electronics. These systems are used for patient care, for clinical and basic research, and for the education of clinical associates in the use of computers in medicine.

A large, computer-based Medical Information and Communication System is used in support of patient care in the Clinical Center. One hundred and forty display terminals and 67 printers are located on the Clinical Center nursing units and in-service department areas to permit rapid retrieval of patient information and processing of medical orders. This system is used by physicians, nurses, and other medical professionals as part of their daily patient care activities. In addition, information obtained during the patient care process is available through the central NIH computer facility for retrieval and research analysis.

The Clinical Center admits approximately 7,500 patients yearly. In addition, the outpatient clinics service over 100,000 patient visits annually.

A new 13-story Ambulatory Care Research Facility is being constructed to expand and strengthen the laboratory and patient care programs of the Clinical Center. The ACRF will provide an optimum environment to study diseases such as cancer, heart disease, and neurological disorders. It will allow patients to carry on nearly normal daily lives while being studied and treated. When this new addition to the Clinical Center opens in 1981, it will accommodate an estimated 200,000 outpatient visits each year.

The Clinical Center appoints clinical associates for the Departments of Diagnostic Radiology, Blood Bank, Clinical Pathology, and Nuclear Medicine. These programs are described in part three.

The Associate Training Program

Opportunities for training and experience in clinical and laboratory investigation are available to physicians and dentists through appointments as clinical, research, or staff associates at the National Institutes of Health. These positions encompass most medical specialties and basic science disciplines.

Appointments to the Associate Training Program are based on professional attainment, research interest, and ability. *The NIH seeks outstanding candidates and selection is made without regard to race, geographical location, or university affiliation.* Candidates may be selected because of demonstrated excellence in research or in a clinical discipline. Selections are made through a matching process, explained in part two.

Each associate participates in a research program under the direction of a preceptor. Preceptors, drawn from a large number of skilled investigators, serve to enrich each associate's experience. Because of the unique blending of clinical and nonclinical scientists, the associate is in daily contact with scholars representing a variety of research interests.

The NIH offers many educational opportunities ranging from tutorial to sponsored lectureships open to all Institutes. Postgraduate instruction, sponsored by the Clinical Center or the graduate program of the Foundation for Advanced Education in the Sciences, Inc., is available on a broad range of topics, including mathematics, languages, laboratory skills, and clinical reviews (see part four).

A candidate may enter the Associate Program as a member of the United States Public Health Service Commissioned Corps or as a civilian employee.

The Clinical Associate
The NIH affords the clinical associate the opportunity to participate in clinical and laboratory research. Clinical activities are carried out near laboratory facilities and are under the immediate supervision of senior investigators. This proximity to patients and to collaborating scientists from many biological disciplines has created a superb environment for learning and performance of clinical research.

The Research Associate
The research associate devotes most of his or her time to laboratory research in a biomedical science. The preceptor is responsible for training in research methods and design, and for guidance in the conduct of specific research undertakings and in the interpretation of results. One of the goals of the program is to select research problems which will enable the associate to gain breadth and perspective, encounter a variety of laboratory problems, and learn many different approaches rather than become a specialist in one or two refined techniques.

The Dental Clinical Associate
Like physician clinical associates, the dental clinical associate may participate in laboratory and clinical research, and enhance professional skills by treating Clinical Center medical and dental patients in the Dental Clinic of the National Institute of Dental Research.

During the 2-year tenure of the associateship, there is full opportunity for an associate to become familiar with all ongoing research programs relevant to dentistry; affiliate with one or more preceptors to participate in a mutually acceptable area of investigation; and extend scientific background through rounds, conferences, seminars, and formalized course work.

The Pharmacology Research Associate
Sponsored by the National Institute of General Medical Sciences, pharmacology research associates spend

most of their time in laboratory research. They may receive intensive research training in any of several disciplines related to modern pharmacology. They also attend formal seminars and informal discussion groups which provide an opportunity to become acquainted with a range of pharmacological research and to meet other scientists active in this area.

The program is intended for those committed to pharmacology or toxicology by training or research and for those who wish to acquire specialized experience in the field of pharmacology.

The Staff Associate

The staff associate position provides opportunities for those highly qualified candidates who could contribute significantly to research areas not specifically designated in the research or clinical associate categories. The staff associate may participate in either laboratory or clinical research or both, depending upon the activities of the senior investigator with whom the associate works. Research experience may be supplemented by attending formal evening study courses, lectures by guest speakers and a variety of medical seminars.

Staff Physicians

Some physicians, already qualified in a specialty, are not appointed as associates, but as staff physicians. Initial appointments are temporary and usually for 2 years, but some staff physicians are later invited to join the permanent staff. Rather than training in research, their primary responsibilities are to provide specialized essential services such as radiology and anesthesiology. However, there are also opportunities to participate part-time in research.

Clinical Electives for Medical Students

The National Institutes of Health conducts a program of elective courses open to students from any of the nation's medical schools. For 1981-82, the staffs of several Institutes are collaborating to supply an in-depth exposure to 11 clinical subspecialties: anesthesiology, computers in clinical medicine, endocrinology and metabolism, genetics, immunology, medical-surgical neurology, nuclear medicine, oncology-hematology, psychopharmacology, pediatric psychopharmacology, and surgical oncology.

The essence of this educational experience is close association between the student, clinical associates, and physician-scientists in several of the Institutes.

Students are assigned patients for workup, discussion, and participation in the pertinent studies. Special rounds and conferences are held with students. Also, students are encouraged to take part in all regular clinical and research conferences, and journal clubs.

Tutorials for individual students with interests in fields other than those listed above are sometimes arranged through communication between an NIH staff member and a faculty sponsor of the students.

Requests for a descriptive catalog and information concerning application for an elective should be addressed to:

Associate Director
The Clinical Center, Room 1N206
National Institutes of Health
Bethesda, MD 20205

Approved Training Programs

Residency training programs approved by the Liaison Committee for Graduate Medical Education are offered in anatomical pathology, clinical pathology, nuclear medicine, blood banking and immunohematology.

Requests for information and application forms regarding these programs should be addressed to the respective program chiefs:

Ronald J. Elin, M.D., Ph.D.
Chief, Clinical Pathology Department
Clinical Center
National Institutes of Health
Bethesda, MD 20205

Jose Costa, M.D.
Chief, Laboratory of Pathology
Clinical Center
National Institutes of Health
Bethesda, MD 20205

Paul V. Holland, M.D.
Chief, Blood Bank Department
Clinical Center
National Institutes of Health
Bethesda, MD 20205

Gerald S. Johnston, M.D.
Chief, Nuclear Medicine Department
Clinical Center
National Institutes of Health
Bethesda, MD 20205

Board Certification: The American Board of Internal Medicine will grant 1 year of credit for 3 years of associate training with the National Heart, Lung, and Blood Institute. The 3-year Clinical Associate Program has been accepted for training by the subspecialty board in Infectious Diseases and the conjoint Board of Allergy and Immunology.

Partial credit towards Board certification is offered in the following specialties and subspecialties:

Cardiology
Dermatology
Endocrinology
Internal Medicine (NHLBI)
Medical Oncology
Neurology
Nuclear Medicine
Pediatric Oncology
Pediatrics
Psychiatry
Rheumatology

Candidates are advised to consult the appropriate institute and specific subspecialty board for additional information.

Endocrinology Fellowship Program

The NIH Endocrinology Fellowship Program is an interinstitute program which involves most of the clinical branches working in this field on the campus at Bethesda. It is devised for physicians who seek a broad experience in both fundamental research and clinical experience in endocrinology. Fellows are selected for a period of 2 or 3 years which includes approximately 1 year of clinical activity among several endocrinology branches of the NIH. During this clinical period, fellows function as primary care physicians for the 70-bed endocrinology inpatient services, serve as consultants for other services of the 540-bed Clinical Center as well as for other local hospitals, and participate in outpatient work, rounds, and seminars. The remainder of the time is spent primarily in laboratory investigation under the direction of a senior investigator in one of the endocrinology branches. During this research period opportunity exists for continuing outpatient work and participation in clinical conferences. No position will be offered for a single year.

Clinical associates selected by any of the three endocrinology branches of the National Institute of Arthritis,

Metabolism, and Digestive Diseases (Clinical Endocrinology, Diabetes, or Metabolic Diseases) and the Endocrinology and Reproduction Research Branch of the National Institute of Child Health and Human Development automatically participate in the interinstitute program. Associates from other branches may participate only under special circumstances. The National Heart, Lung, and Blood Institute also participates in the interinstitute program.

Lectures and Courses

The NIH campus provides a stimulating intellectual environment for continuing education, including multiple clinical and basic science conferences and journal clubs, as well as tutorial seminars and courses spanning many disciplines. This Fellowship Program sponsors formal endocrinology seminars and lecture series covering the field broadly and in detail. The Computer Science Division and Radiation Safety Branch provide detailed practical work and study in these fields. The latter branch gives an intensive course in the use of radionuclides, enabling graduates to apply for their own radioisotope license after completion of the fellowship.

Medical Student Program

Students selected from various medical schools throughout the country participate in endocrinology courses offered 3 times yearly. Fellows work in close association with the students and supervise their patient care activities. These and other teaching functions help develop the fellows' skills as educators in preparation for later academic careers.

Internal Medicine and Endocrinology Board Examinations

Studies in the Clinical Center relate to all areas of internal medicine, and fellows are encouraged to develop their general clinical skills. Completion of the Fellowship Program satisfies requirements for the Endocrinology Subspecialty Board Examination. Because of recent changes in the requirements for the Certifying Examination of Internal Medicine, applicants are encouraged to review their residency training plans directly with the Board.

Prospective applicants who would like further information on the program should write Dr. Bruce D. Weintraub, Building 10, Room 8N315, National Institutes of Health, Bethesda, Maryland 20205.

Medical Genetics Fellowship Program

The NIH Interinstitute Medical Genetics Fellowship Program is a cooperative undertaking involving several clinical branches and research laboratories in 6 Institutes located on the Bethesda campus. It is a program of 2, or in some cases, 3 year duration for physicians seeking broad exposure to both research and clinical experience in human genetics. The training is also designed to fulfill all requirements proposed by the American Society of Human Genetics for fellowships leading to eligibility for board certification in medical genetics.

The first year of the Fellowship includes clinical activities and initiation of laboratory or clinical investigations under the direction of a senior scientist. Fellows will be responsible for patients seen at the weekly NIH Genetics Clinic and the NIH supervised Prenatal Diagnosis Clinic at George Washington University Hospital. They will also serve as genetics consultants in the 540-bed Clinical Center and will participate in conferences, rounds and seminars. Further opportunity to become familiar with the spectrum of patients with genetic disease is provided by optional attendance at genetics clinics at collaborating institutions including the Children's Hospital-National Medical Center in Washington, D.C. and the Johns Hopkins Hospital in Baltimore.

The second year of the Fellowship will primarily involve research activities initiated during the first year. Fellows may elect to pursue research chosen from many types of investigations related to genetic diseases; descriptions of the diverse interests of participating scientists are provided in a brochure which will be supplied to fellowship applicants. The NIH program aims to provide fellows with research experiences of the highest caliber and to prepare them for careers as independent investigators in human genetics.

The Fellowship Program includes a formal seminar series in medical genetics in which invited speakers discuss research and clinical topics of current interest, and other opportunities for continuing education (clinical and basic science conferences, journal clubs, tutorial seminars, and postgraduate courses) are plentiful on the NIH campus. The Fellowship Program also sponsors a yearly 8-week elective in medical genetics for senior students from medical schools around the country; fellows assist in didactic lecture-demonstrations on the approach to patients with genetic diseases and in supervision of students in patient related activities. These and other teaching opportunities develop the fellows' skills as educators in preparation for future academic careers.

Applications for the Fellowship Program should be directed to the Associate Office (see p. 9). Further information may be obtained by telephone from Dr. Joseph D. Schulman at (301) 496-6683.

Part Two

Applying for an Associateship

About 100 clinical associates and 50 research and staff associates are appointed annually. Associates may be employed through the Commissioned Corps of the Public Health Service or as civilian employees through the Office of Personnel Management.

Minimum eligibility requirements for most associateships is completion of 2 years of graduate medical training before entrance on duty. Application should be made between 1 and 2 years before desired date of appointment.

To be considered for a clinical, research, or staff associate appointment, completed application forms must be received in the NIH Associate Office, Building 31, Room 4B04, National Institutes of Health, Bethesda, MD 20205 by February 6, 1981.

Participants of the Public Health Service Scholarship Program are not eligible for consideration until after they have served obligated pay-back years in designated PHS programs where a shortage of physicians exists.

Public Health Service Commissioned Corps

The Commissioned Corps is a uniformed service similar in many respects to the Army, Navy, and Air Force. It is an "all officer" Corps, comprised largely of professionals in medical and health related fields.

Pay, allowances, and other benefits are comparable to those of officers of the Armed Forces. Benefits include medical care for officers and dependents; tax-free allowances for quarters and subsistence; commissary, post exchange, and officers' club privileges; and 30 days annual leave.

While most career PHS officers are eligible for the variable incentive pay (VIP) "bonus," VIP is not an immediate incentive to prospective associates. Officers serving in their first 2 years as associates, are *not* eligible for VIP.

For those considering longer periods of service or careers in the PHS, the advantages of subsequent VIP, and of noncontributory retirement and survivor benefit plans are substantial.

To be eligible for the Commissioned Corps for participation as an NIH associate, a candidate must meet the following requirements:

- be a United States citizen.
- meet the medical fitness standards.
- be a graduate of an accredited medical or dental school.
- satisfactorily complete an internship approved by the Council on Medical Education. (However, application will be accepted when internship is an integral part of medical school curriculum or incorporated as part of residency training.)

Application forms to the PHS will be mailed to applicants selected as associates.

Civilian Staff Fellowships

As an alternative to the Commissioned Corps, associates may be appointed as staff fellows. This is a temporary civil service appointment. Salaries are similar to those Commissioned Corps officers who do not receive the variable incentive pay "bonus." Medical fitness standards are less stringent, and noncitizens of the United States who are eligible for naturalization within 4 years may be appointed. Usually, fellows earn slightly less annual leave. Comparative advantages of retirement plans and fringe benefits depend largely on individual circumstances and preferences.

Method of Selection—Matching Program

Selections for the clinical, research, and staff associate appointments are made through a matching process in which the candidate's preferences are matched with the Institute's preferences.

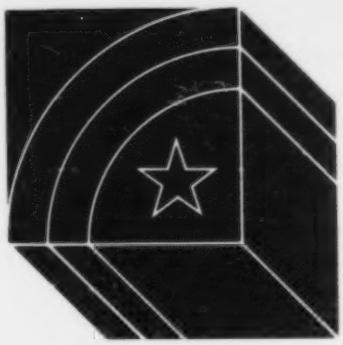
In the application packet, a candidate will find several sheets, each headed "Program Area Selection Check List." After reading part three of this catalog, the candidate should check off on these sheets the areas in which he or she is interested. There is no limit to the number of interest areas which may be checked. The application will be sent to all laboratories and branches which the candidate has checked.

After thorough review of all applications by the Institutes, a limited number of candidates will be selected for personal interviews after which the candidate submits his or her confidential preference list. *Applicants should only list programs in which they have an interest and would accept if chosen. In a highly competitive selection system, failure to accept a position after the "match" compromises another candidate's opportunities.*

The NIH Associate Office will set up the interview and advise candidates when to report. Candidates are requested not to attempt to arrange their own interviews.

Part Three

Program Areas for Which Candidates May Apply



Each of the major NIH components has prepared a description of its program areas for which associates may seek appointment. These descriptions are meant to anticipate many of the questions applicants may have in selecting program areas for which they wish to be considered. *It should be noted that a candidate is not limited as to the number or kinds of positions for which he or she may apply.*

National Cancer Institute

Vincent T. DeVita, Jr., M.D.,
Acting Director, Clinical Director

Division of Cancer Biology and Diagnosis—Alan S. Rabson, M.D., Director.

The Division of Cancer Biology and Diagnosis is broadly concerned with biochemical, genetic, physiologic, immunologic, and metabolic derangements that predispose organisms to neoplasia and that result from neoplasia. Within this area, a wide variety of research interests are pursued which involve basic questions of immunology, virology, molecular biology, and biochemistry of normal and pathologic states. The Division is composed of several branches and laboratories, each under the direction of a branch or laboratory chief.

Clinical and research associate positions are available in many of these areas and associates work exclusively with the branch or laboratory in which they are accepted. Both clinical and research associates have a unique opportunity to become experienced scientists in their fields of interest and thereby initiate a career in academic medicine and research.

Clinical Associates

Clinical associate positions are available in the Metabolism Branch, Immunology Branch, Dermatology Branch, and the Laboratory of Pathology. Clinical associates participate in patient care directly related to the research interests of the branch and engage in general research under the direction of individual scientists. The scope and orientation of each of these positions depends, of course, on that of the particular branch or laboratory.

Research Associates

Research associate positions are available in the Laboratory of Biochemistry, the Laboratory of Pathophysiology, the Laboratory of Molecular Biology, and the Laboratory of Immunodiagnosis.

In general, research associates are engaged in original research under guidance of individual investigators who act as preceptors for the associates.

Clinical Research Branches

Dermatology Branch—
Dr. Stephen I. Katz

The Dermatology Branch studies the growth and differentiation of epithelium and lymphoreticular tissues in normal, hyperplastic and neoplastic states; protein synthesis by epithelium, espec ally of tonofilaments, keratohyalin and actin; immunologic determinants of tissue behavior in normal and neoplastic states; immunologic abnormalities in blistering diseases of the skin; physiology of lymphoreticular cells and lymphokine formation; and the biological activity of oncogenic viruses.

Also studied are experimental allergic contact dermatitis; scanning and transmission ultrastructure of normal and diseased skin and other tissues; scanning microscopy of the cell surface structure in relation to the mitotic cycle and motility; genodermatoses; biochemical and ultrastructural aspects of melanogenesis in normal and melanoma tissue; biochemistry and keratinization; xeroderma pigmentosum, an inherited disease of sun sensitivity, and multiple cutaneous cancer with abnormal DNA repair; chemical and ultrastructural effects of vitamin A on skin; the oncogenic potential of tumor viruses; the development of therapy of epithelial cancers, skin lymphomas and keratinizing diseases of the skin.

Immunology Branch—
Dr. William D. Terry

The branch is concerned with the chemistry, genetics, biology and clinical significance of immunity. Cellular immunity, transplantation immunity, and the nature of mammalian cell surfaces are the fundamental areas developed within the branch. Information derived from these areas is applied to studies of the relationship between the immune system and neoplastic cells in experimental animals and man.

Cellular Immunity—Cell-mediated immune reactions as assessed *in vitro* by T-cell-mediated lympholysis and mixed lymphocyte reactions are being studied; tumor growth is being studied *in vivo* in murine models. The role played by the major histocompatibility complex (MHC) both with respect to MHC-product-associated immunogenic complexes and to immune response genes controlling reactivity to these immunogenic complexes is under investigation. The nature of regulatory influences on cell-mediated immune responses to transplantation antigens is being investigated. Further work is being done on the mechanism of such regulatory influences, the role and expression of products of the I region of the MHC in these events, and the potential relevance to *in vivo* phenomena including transplantation and tumor immunity. The mechanisms by which immune, as well as nonimmune lymphoid cells kill specific target cells are also under investigation. The receptors for immune complexes (Fc receptors) on certain immunocompetent cell populations are being characterized by a variety of methods.

Humoral Immunity—A primary

IgM plaque-forming cell assay and a T-cell proliferation assay have been developed and characterized in the mouse for use with a variety of antigens including those under genetic control. These assays are being used to evaluate the cellular level of expression of immune response genes and the mode of action of such genes; to evaluate the role of cell surface antigens determined by the I region of the H-2 complex and the rate of subpopulations of cells bearing these antigens; to characterize the nature and mechanism of action of antigen-specific helper and suppressor factors; and to evaluate the immunologic role of idiotype-bearing molecules of both T- and B-lymphocyte origin.

Transplantation Immunity—Antibodies against histocompatibility antigens and tumor antigens are used as reagents for determining the nature of these antigens and manipulating the immune response against them.

Antibodies with specificities directed against transplantation antigens are being examined for chemical and immunologic individuality. Mouse lymphocyte alloantigens determined by genes in the Ir region (Ia antigens) are being studied serologically and functionally. The effect of immune response genes on the response to transplantation antigens is being studied and anti-idiotype sera to receptors for transplantation antigens are being characterized.

Cell Membranes—The chemistry of lymphoid cell membranes is being investigated in an effort to characterize the molecular makeup of surface components and to identify and study specific functional receptors. Simple defined membrane systems are being designed to model immunologic phenomena such as cell-mediated cytotoxicity and patching and capping of surface antigens. The mechanisms whereby cells of the immune system damage or kill target cells and the nature of the membrane alterations involved are also being studied.

Molecular Immunology—The structural organization of the genes encoding the MHC products and the regulation of the expression of these genes are beginning to be studied. *In vitro* synthesis of MHC products has been accomplished, which will allow further investigation of the biosynthesis, maturation, and insertion into the cell membrane of the MHC products. Isolation of the genes encoding the MHC products involved in immune responses and the transplantation antigens is currently in progress.

Immunochemistry—The structural and biological consequences of antigen-antibody interactions are being examined by using affinity cross-linked oligomers of IgC antibodies as models for naturally occurring immune complexes.

Tumor Immunology—Cellular immune mechanisms of tumor-bearing animals and patients with a variety of malignancies are studied and attempts are made to modify reactions so as to improve tumor cell kill. Specific assays are established to determine the presence of humoral and cell-mediated responses of hosts to tumors.

Immunotherapy of tumors is approached, both in animal models and patients, through the use of nonspecific and specific stimulation of the immune system. A clinical study is now in progress to evaluate the effectiveness of adjuvant therapy in preventing recurrence of malignant melanoma in patients who have been rendered clinically free of disease, but who have poor prognosis in the absence of therapy.

Metabolism Branch—
Dr. Thomas A. Waldmann

- Immunophysiology Section—Dr. Warren Strober
- Cellular Immunology Section—Dr. R. Michael Blaese
- Endocrine Section—Dr. James M. Phang

The Metabolism Branch is broadly concerned with clinical and labora-

tory studies which focus on the immunologic, endocrinologic and metabolic bases of disease occurring in patients with neoplasia.

Immunologic interests encompass studies of immune regulation, including factors controlling helper and suppressor T-cell function in immunodeficiency states (hypogammaglobulinemia, IgA deficiency, Wiskott-Aldrich syndrome, and ataxia telangiectasia), in leukemias of T-cells as well as in animal models of disordered immunity. Other areas of immunologic interest include studies of the genes controlling immunoglobulin synthesis and their organization, and studies of the genetic basis of immunity, including the relationship between HLA antigens and disease (gluten-sensitive enteropathy) and genetic factors controlling the response to complex chemically defined proteins; studies of cytotoxic effector mechanisms and the role of macrophages in the afferent and efferent limb of the immune response; studies of gastrointestinal (GI) tract immunology, including the investigations of intestinal lymphangiectasia GI allergy, and GI abnormalities associated with immunodeficiency; studies of patients with lymphoproliferative neoplasms including multiple myeloma and chronic lymphocytic leukemia; and T-cell leukemias including Sézary syndrome, with the aim of defining the T-cells with retained immunologic functions.

Endocrine interests include biochemical studies of amino acid metabolism related to collagen synthesis and gluconeogenesis (studies of regulation of enzymes in the collagen synthetic pathway and the proline degradative pathway). These are related to studies of patients with disorders of metabolic bone disease, diabetes mellitus and amino-acidopathies. Studies of growth hormone, somatomedin and other growth peptides are related to studies of patients with growth disorders, and work on factors regulating porphyrin metabolism include experimental treatment of patients with various forms of porphyria.

Basic Research Laboratories

Laboratory of Biochemistry—Dr. Maxine Singer

The emphasis of the work in the Laboratory is on the relation between structure and function in biological systems and on the regulation of cellular processes. The research involves prokaryotes and a range of eukaryote systems selected because of their potential for yielding important information on cellular structure, function, regulation, development, and differentiation. The study of regulation encompasses regulation of gene expression, regulation by interaction of macromolecules, and regulation of cells by hormones and ions. Work is carried out on both the molecular and cellular level. Techniques include those of biochemistry, physical chemistry, cell biology, and molecular genetics.

- Biochemistry of Gene Expression Section—Dr. E. Brad Thompson

Control of gene expression in eukaryotic cells and its application to clinical medicine are studied. The effects of steroid hormones on enzyme induction in cultured cells and cell hybrids are investigated, along with studies on steroid receptors in human leukemia and breast cancer. The molecular details of steroid action are rapidly being learned, providing an excellent model for studying the general question of gene expression in animal cells. In this section, a combination of cell genetic—variant cell lines, hybrids—and biochemical techniques—mRNA translation, RNA and DNA analysis, DNA cloning—are being used. Clinical applications are made when feasible.

- Biosynthesis Section—Dr. Edward L. Kuff

Studies on molecular and func-

tional properties of tumor virus nucleic acids, the enzymatic mechanism of DNA synthesis, and the regulation of collagen biosynthesis and secretion in normal and transformed cells are the concern of this section. Technical approaches include analysis of nucleic acid sequence relationships and genomic organization, isolation of subcellular and viral components, purification of DNA polymerases and their use in constructing *in vitro* synthetic systems, and the characterization of enzymes and cofactors involved in sequential processing of newly formed collagen.

• Cellular Regulation Section—Dr. Robert F. Goldberger

Mechanisms of regulation of gene expression at the molecular level in eukaryotic organisms are investigated, with special emphasis on induction of specific proteins by steroid hormones and the arrangement of specific genes in the genome. One of the systems under investigation is the estrogen-induced synthesis of the egg yolk phosphoprotein, vitellogenin, in rooster liver. *In vitro* transcription of chromatin and nuclei is used to study the effects of hormone on gene expression at the molecular level. Techniques involving recombinant DNA molecules are utilized to obtain structural information about the genes under study and about the genomic environments of those genes. *In vitro* transcription is studied utilizing DNA-dependent RNA polymerase and a variety of DNA templates. Conditions required for accurate initiation of RNA synthesis are under study.

• Developmental Biochemistry Section—Dr. Igor B. Dawid

Studies on the biochemical processes in development and differentiation are investigated with particular emphasis on regulatory phenomena. The structure of selected components of the genome of several animal species are studied, as well as gene expression during the development of germ cells and embryos. Currently under study are the mitochondrial genome of frogs, certain nuclear genes active in early frog embryos, and the ribosomal genes of *Drosophila*.

• Macromolecular Interactions—Dr. Claude B. Klee

Studies are directed toward the understanding of the mechanism of coupled regulation of cellular processes by Ca^{2+}, calmodulin and cyclic nucleotides. Enzymes regulated by calmodulin are characterized and then interaction with calmodulin and other regulatory ligands are studied at the molecular level as well as in eukaryotic cells in tissue culture.

• Nucleic Acid Enzymology Section—Dr. Martin Rosenberg

Studies pertain to a variety of nucleic acid structural and functional relationships involved in the regulation of cellular and viral gene expression in both prokaryotic and eukaryotic systems. Of particular interest are those protein-nucleic acid interactions involved in the transcription and translation of mRNA, the organization of mammalian DNA, the origin, structure, and biology of defective simian virus 40 and its DNA.

• Protein Chemistry Section—Dr. Elbert A. Peterson

Proteins and subcellular particulates involved in synthesizing, controlling, and differentiating systems of biological organisms are investigated. Studies are in progress on the biochemical changes accompanying differentiation and maturation of leukocytes and the nature of humoral factors controlling these processes; the isolation and subfractionation of chromosomes and their use in the biological transfer of genetic information; the interactions between cells involved in the immune response; and the development of new physical and immunological methods for the isolation of cell types, organelles, and macromolecules of interest.

Laboratory of Cell Biology—Dr. L. W. Law

Personnel of this laboratory have

diverse interests focusing upon the study of transformation of a normal cell to a neoplastic cell. Some of the specific problems pursued are: genetic control of the synthesis of abnormal proteins produced by malignant cells, principally plasma cells; role of cell membranes in regulating differentiation and growth; identification and study of tumor antigens and of the specific immune reactions initiated; solubilization and purification of transplantation and tumor antigens; influence of somatic cell hybridization on expression of genetically determined events; and ultrastructural analysis and molecular biology of viral oncogenesis. Techniques from virology, immunology, immunochemistry, biochemistry, biophysics, tissue culture, somatic-cell hybridization, and electron microscopy are used in these studies.

- Office of the Chief

Investigations are conducted in collaboration with the chemistry unit on the biologic, biochemical, and chemical characteristics of solubilized and purified H-2, HL-A and tumor antigens on the cell membrane. Studies are also in progress on the immune response of the tumor-bearing animal and response to solubilized tumor antigens.

- Somatic genetics unit—Dr. H. C. Coon

This unit is studying the genetics and transforming capacity of mitochondrial DNA and the characteristics of somatic cell hybrids, particularly those employing neuron hybrids.

- Chemistry unit—Dr. E. Appella

Biochemical, biophysical, and chemical studies are conducted on solubilizing and purifying tumor antigens and histocompatibility antigens (H-2, HL-A). The unit is also investigating the epoxide hydrase mechanism in the metabolism of chemical carcinogens, the chemistry of Edman degradation, and new supports for solid phase degradation.

- Cell-mediated immunity studies unit—Dr. C. C. Ting

This unit studies mechanisms of tumor cell killing in syngeneic systems using several cell-mediated assays; also the role of humoral factors, suppressor cells, and helper cells.

- Immunochemistry Section—Dr. M. Potter

This section focuses on the chemistry of immunoglobulins secreted by plasma cell tumors; the factors concerned with initiation and growth of myelomas; and the antibody combining sites of myeloma proteins.

- Ultrastructural Biology Section—Dr. N. A. Wivel

Laboratory investigations focus on factors that contribute to cell differentiation and malignant transformation with particular emphasis on systems where oncogenic viruses represent the carcinogenic agent.

- Viral Oncogenesis Section—Dr. Kenneth S. S. Chang

In vitro and *in vivo* systems are used to study the interaction between oncogenic viruses, principally RNA-contained, and host cells with special attention directed to host specificity; the genetic factors influencing susceptibility; the role of endogenous viruses in the etiology of reticulum cell sarcomas; and the characterization of features that distinguish viral structural antigens from tumor-associated antigens in the leukemias.

Laboratory of Immunobiology—Dr. Herbert J. Rapp

- Section on Cellular Immunity—Dr. Herbert J. Rapp

Cell-mediated immunologic reactions are studied for their capacity to inhibit the growth and spread of experimental cancers. A variety of animal and *in vitro* models are being used in attempts to delineate the mechanisms of these reactions.

- Section on Humoral Immunity—Dr. Tibor Borsos

Antibody and complement mediated cytotoxic reactions are studied for the mechanism of action. The primary goal is to understand the molecular basis of complement action

and the molecular basis of cell defense mechanism against complement attack. Purification of antibodies, complement components, cell membrane receptors and studies of synthetic pathways that control cell membrane integrity are also part of the study.

- Section on Immunopathology—Dr. Edward J. Leonard

Alterations in cellular immune function in pathological conditions are studied. Projects include mechanisms of macrophage activation, serum factors that alter macrophage function, the nature of depressed mononuclear phagocyte chemotaxis in patients and animals with neoplasms, the mechanisms of basophil accumulation in delayed hypersensitivity reactions, and the production and chemical nature of lymphotoxin.

Laboratory of Molecular Biology—Dr. Ira Pastan

- Section on Biochemical Genetics—Dr. Max Gottesman
- Section on Gene Regulation—Dr. Benoit de Crombrugghe
- Section on Cell Organization—Dr. Seymour Wollman

A major focus is on how genes function to control cell behavior. Attention is devoted to the genetic and biochemical alterations that occur when normal cells are transformed to cancer cells by tumor viruses and to alterations in cyclic AMP, cell surface protein and collagen synthesis. The tools of somatic cell genetics, including mutant isolation, karyotyping and chromosome transfer, are extensively employed. Certain genes, such as the *src* gene of Rous sarcoma virus and collagen, whose synthesis is altered by the *src* gene in malignant transformation are cloned in *Escherichia coli* by recombinant DNA techniques to permit analysis of their altered expression in cancer cells. Studies are carried out on cellular ultrastructural organization that enables movement, phagocytosis, pinocytosis, and mitosis. The section studies genetic elements involved in the control of transcription initiation and termination, the mechanism of excision and integration of viral genomes and the initial steps in the replication of the DNA of some DNA coliphages.

Laboratory of Pathology—Dr. Alan S. Rabson

- Surgical Pathology and Postmortem Section—Dr. Jose Costa
- Hematopathology Section—Dr. Costan W. Berard
- Cytopathology Section—Dr. Elizabeth W. Chu
- Comparative Oncology Section—Dr. Clyde J. Dawe
- Quantitative Cytology Section—
- Ultrastructural Pathology Section—Dr. Timothy J. Triche
- Viral Oncology and Molecular Pathology Section—Dr. Peter M. Howley
- Pathological Technology Section—Barbara Coolidge

The laboratory offers a 2- to 4-year training program for residents in pathologic anatomy. This program, which is fully approved for Board certification, provides well-supervised instruction and experience in the performance of autopsies, surgical pathology, and exfoliative cytology. Special training in the subspecialties of cardiac pathology, hematopathology, and neuropathology can be arranged. Opportunity is provided for learning many research techniques, particularly electron microscopy, fluorescence microscopy, tissue culture, histochemistry, autoradiography, and cytogenetics. Individual or collaborative participation in clinical or laboratory research projects by the residents and selected research fellows and visiting scientists is encouraged.

In addition, the laboratory offers research training in experimental pathology. Research projects include studies of oncogenic viruses and viral carcinogenesis, chemical carcinogenesis, immunopathology and tumor immunology, experimental embryology as related to cancer, and biochemical and ultrastructural studies

of viruses and neoplastic cells.

Laboratory of Pathophysiology
—Dr. Pietro M. Gullino

A group of projects concerning the mammary gland is carried on in connection with the Office of the Chief. Dr. Cho-Chung works with the mechanism of hormone dependent mammary tumor regression, Dr. Knazek studies the mode of prolactin action on target organs, Dr. Vonderhaar evaluates the role of thyroid on mammary tumor development, Dr. Qasba correlates the synthesis of secretory proteins during growth and regression of normal and neoplastic gland, Dr. Liotta measures production and defines the characteristics of collagen production and turnover of mammary collagen, and Dr. Gullino works on the angiogenic properties of hyperplastic and neoplastic mammary epithelium.

- Section on Cellular and Molecular Physiology—Dr. Herbert L. Cooper

This section studies the biochemical mechanisms that control early stages of cell growth induction in normal and neoplastic human cells. Emphasis is on the mechanisms which maintain physiologically resting cells in the non-growing condition and the early biochemical modifications that occur on growth stimulation. Current studies include characterizations of translational controls in resting human lymphocytes, and examination of certain facets of messenger RNA metabolism which are unique to physiologically resting cells.

- Section on Cell Cycle Regulation
—Dr. William Kidwell

Laboratory investigations are concerned with the characterization of biologic events uniquely required for the cell to progress through S, G_2, M, G, and G_0 phases. Emphasis is placed on the nutritional, hormonal and other factors involved in initiation of cellular transition through division to a differentiated state and the interrelationship among various organ cell types in this progressive change.

- Section on Membrane Biology
—Dr. Pedro Pinto da Silva

Studies in this section are on the structure, dynamics and function of biological membranes through transmission. Scanning electron microscopy of freeze-fractured, freeze-etched and immunochemically labeled plasma membranes are used in these investigations.

- Section on Energy Metabolism—

Laboratory studies here concern the physiological and behavioral control of energy exchange and of food and water intake and its relation to cancer cachexia.

- Section on Radiation Biology

The section is involved in the use of radiation to destroy bone marrow in order to study the laws governing marrow transplantation from donors. The effects of ionizing and UV radiation on nucleic acids and proteins are also being studied.

Laboratory of Theoretical Biology
—Dr. Mones Berman

The laboratory is concerned with the formulation of theories of structure, function, and dynamics of biological systems, with the development of models for these systems, and with the development of mathematical and computational techniques for modeling and data analysis. Several areas are of particular interest: kinetics of metabolic systems and therapeutic agents; membrane structure and function, including transport through artificial lipid bilayer membranes, interaction of lipid vesicles with cells, and mobility of cell surface components; receptors and hormonal regulation; immune response systems and carcinogenesis; configurations and properties of polypeptides and other macromolecules. Although the work is predominantly theoretical, experimental studies related to these problems are carried out within the laboratory and in collaboration with others.

Division of Cancer Treatment—Dr. Vincent T. DeVita, Jr., M.D., Director

An intensive program of laboratory research and clinical investigation concerned with cancer therapy is the responsibility of the Division. Emphasis is placed on combinations of drugs with other modalities of therapy including surgery, radiation, and immunotherapy.

Cancer Therapy Evaluation Program—John S. Macdonald, M.D., Associate Director

Staff Associates

Two staff associate positions are open each year within the Cancer Therapy Evaluation Program. These associates are assigned to the Investigational Drug Branch for 1 year. Subsequently, a second year program may be developed in conjunction with other branches or laboratories within the Division of Cancer Treatment, or within the Cancer Therapy Evaluation Program by rotating to the Clinical Investigations Branch. It is anticipated that the second year associate will also maintain some responsibility for drug monitoring. Eligibility for a third year within the program is feasible. The duties within the Investigational Drug Branch include monitoring drugs within the Drug Evaluation and Reporting Section; usually, 10 to 20 drugs are assigned to one associate. Some concentration in specific areas may be possible. The work within the Clinical Investigations Branch usually consists of assisting coordinators and project officers in disease-oriented programs. These include helping develop disease-oriented strategy, coordinating contract groups, assisting in protocol review, and planning discussion groups and intergroup studies.

The major function of the Cancer Therapy Evaluation Program is to sponsor clinical trials of investigational and known antineoplastic treatment modalities and to monitor those trials. The scope of the program has evolved from broad drug trials with investigational chemotherapeutic agents to a disease-oriented approach. This includes the incorporation of effective chemotherapeutic combinations during early stages of disease and testing of new modalities, such as immunotherapy in combination with surgery, radiotherapy, and chemotherapy in specific disease entities, until now considered untreatable. For these purposes, the program has planned and helped organize several study groups as part of a Clinical Contract Program designed to test combined modality approaches to specific diseases. The program also supports, through the grant mechanism, various clinical cooperative groups made up of institutions of higher education. These cooperative groups share in the design, development, execution and analysis of clinical protocols. The program encourages and sponsors disease-oriented meetings with representatives from all interested groups to achieve coordination of clinical research effort at a national level. This effort is in addition to the interaction with staff members of the program who periodically attend meetings of the clinical contract and cooperative groups, disease-oriented task forces, and working parties. In addition, the program serves as a vehicle of communication between inhouse preclinical and clinical programs and extramural activities.

The program coordinates clinical

conferences sponsored by the chemotherapy area, which is an important mechanism for informing clinical investigators throughout the world on the status of drug trials. The conferences are held to discuss the clinical programs concerned with drug development. The program also maintains a special relationship with the Clinical Oncology Program's branches and the Baltimore Cancer Research Center. In addition, it is responsible for the development of new areas of clinical research and dissemination of information on clinical trials to investigators in foreign countries, and is responsible for receiving and analyzing information from abroad.

Clinical Investigations Branch—Dr. Raymond Weiss

The Clinical Investigations Branch is responsible for monitoring activities of the clinical cooperative oncology groups. Critical review of protocols submitted by the various cooperative groups and updating information on clinical trials within and outside the group programs are major functions. The branch also serves as liaison between group investigators in this country and abroad and the National Cancer Institute. Together with the Cancer Clinical Investigation Review Committee, it sponsors symposia on various aspects of cancer research which are of current importance to clinicians.

The branch is actively involved in initiating contract-supported clinical trials and surveillance on a disease-oriented basis. Moreover, the branch is responsible for the integration and combination of various treatment modalities in therapeutic protocols. The branch has initiated studies using all modalities in gastrointestinal cancer and in testicular cancer from time of diagnosis and is involved in the development of similar approaches for ovarian cancer. The branch is also involved in following the activities of the Breast Cancer Task Force, the Colorectal National Cancer Program, the Lung Cancer Working Party, the Breast Tumor Study Group, the Prostatic National Program, and several international organizations involved in clinical trials.

Investigational Drug Branch—Dr. Vincent H. Bono, Jr.

This branch monitors and coordinates the drug-oriented trials of the Division. The branch serves as a link between the preclinical and clinical aspects of the drug development part of the Division with special interest in the pharmacologic investigations of new drugs. Interaction with investigators is a vital part of the work of the branch in providing supervision, advice, and retrieving information on therapeutic response and toxicity.

- Regulatory Affairs Section—Dr. John S. Penta

The section provides liaison with the Food and Drug Administration and supervises the preparation of all FDA filings on new drugs. This involves a close working relationship with intramural branches and committees dealing with submission of data to meet regulatory requirements.

- Drug Evaluation and Reporting Section

The section reviews, coordinates and monitors protocol studies for phase I and early phase II clinical trials supported under contract. The section prepares annual reports on IND drug studies and investigates and reports on Adverse Drug Reactions for all IND's. It is also responsible for the supervision of drug distribution, whether initiated by cooperative or contract groups or by Cancer Research Centers.

Radiotherapy Development Branch—Dr. David Pistenma

The Radiotherapy Development Branch (RDB) of the Division of Cancer Treatment was created in the NCI reorganization of 1978. Its antecedent was the Radiation Program of the Division of Cancer Research Resources and Centers. The Radiation Program emerged as an identifiable entity in the mid-1960's. In 1972, with the increasing workload, a sec-

ond program director was added, a Program Director for Radiation Biology and Physics to complement a rotating Program Director for Radiation Therapy. In the years since, the program maintained a steady rate of growth and its three major areas of concentration emerged: high LET (linear energy transfer) radiotherapy, hyperthermia, and drugs which modify tissue response to radiation.

The RDB is responsible for administering a recently funded 12 million dollar program in clinical fast neutron radiation and also has component parts including a traditional grant program (RO1) of $14 million and a program project (PO1) grant program of $24 million. The RDB staff also is responsible for the administration of contract-supported clinical research in brain tumors through the Brain Tumor Study Group. The RDB staff includes Dr. David Pistenma, Chief, and Drs. Frank Mahoney, Thomas Strike, and Barrie Jones.

Clinical Oncology Program—Dr. John L. Ziegler, Associate Director

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Clinical Associates

The Clinical Oncology Program recruits approximately 28 clinical associates each year for a 2-year assignment. Associates are recruited for one of the following clinical branches: Medicine, Pediatric Oncology, Radiation Oncology, and Surgery, located in the NIH Clinical Center on the Bethesda campus, or NCI-VA Medical Oncology Branch located at the Veterans Administration Hospital, Washington, D.C.

The 2-year oncology training program is offered to candidates who have at least 2 years of postgraduate training (internship and first-year residency) in medicine, pediatrics or surgery. The first year consists of primary responsibility for the clinical care of both inpatients and outpatients on the assigned branch for a minimum period of 9 months. Three-month elective rotations to other clinical services are encouraged, provided continuity of outpatient care is maintained in the primary branch. The second year consists of clinical and/or laboratory research under the supervision of a member of the senior staff. Clinical electives are available on consultative services in the branches and other related departments, and in various procedures, such as peritoneoscopy. Second-year associates continue to follow patients in the Outpatient Department. Offered throughout the 2-year program are didactic lectures, clinical conferences, research seminars, teaching rounds and joint conferences relevant to the field of clinical oncology and cancer research.

Candidates otherwise qualified who successfully complete the 2-year program are eligible for Board certification in the subspecialty of medical oncology or pediatric hematology-oncology. An additional third year of research is available to selected candidates.

Clinical Pharmacology Branch—Dr. Bruce A. Chabner

This group conducts laboratory and clinical research activities on problems of drug action and toxicity in man, and as such, plays a supporting role for the chemotherapy programs of the other clinical branches of the NCI. The branch does not have patient care responsibilities of its own, but accomplishes its clinical studies through collaborative ties with the other clinical branches. Training opportunities for 1- or 2-year assignments are available for postdoctoral fellows, physicians com-

pleting 1 year of clinical training on a clinical unit at the NCI, or for trainees of the Clinical Pharmacology Training Program of the National Institute of General Medical Sciences.

Areas of specific research interest include: mechanisms of adriamycin cytotoxicity; mechanism of action and cellular pharmacology of antimetabolites; pulmonary metabolism of tissue specific toxins and mutagens; pharmacokinetics and metabolism of established and new antineoplastic agents; clinical and experimental applications of cytofluorometry; and cyclic nucleotide metabolism in human tumor cells.

Medicine Branch—Dr. Robert C. Young

The Medicine Branch is an adult medical oncology unit whose clinical programs emphasize the broad area of internal medicine as related to cancer. Clinical emphasis is given to the diagnosis, staging, and treatment of the malignant lymphomas, Hodgkin's disease, breast cancer, ovarian carcinoma, sarcomas, melanoma, endometrial cancer, chronic leukemias, and testicular cancer. Training in clinical diagnostic procedures such as bone marrow examination, liver biopsy, and peritoneoscopy is emphasized. An active consultation service works closely with other units at NIH, such as cancer surgery and radiation therapy.

The branch conducts weekly clinical conferences with the departments of Radiation Oncology, Pathology, Clinical Pathology (Hematology), and Radiology on current problems and on the staging of lymphomas and Hodgkin's disease. Research focuses on the general areas of kinetics and cytogenetics of neoplastic and hemopoietic cells, immunological alterations induced by disease or chemotherapy, and the biochemical pharmacology of antineoplastic agents. In addition, an active research program is underway in the field of hormone receptors, tumor markers and tissue culture. The branch conducts weekly laboratory conferences, in conjunction with the Clinical Pharmacology Branch, on laboratory topics of mutual interest. Collaboration with the Clinical Pharmacology Branch and other laboratory groups is maintained.

NCI-VA Medical Oncology Branch—Dr. John D. Minna

The NCI-VA Medical Oncology Branch is, while part of the intramural Clinical Oncology Program, located outside the Clinical Center at the Washington Veterans Administration Medical Center (WVAMC) in northwest Washington, D.C. This branch is concerned with the primary care and clinical investigation of patients with a wide variety of solid tumors and hematologic malignancies. A major effort involves the staging and treatment of small cell carcinoma of the lung. In addition to lung cancer, treatment protocols of stomach cancer, prostatic carcinoma, myeloma, mycosis fungoides, and hepatoma are underway. Associates become experienced in diagnostic procedures such as bone marrow biopsy, liver biopsy, fiberoptic bronchoscopy, and peritoneoscopy. Both veteran and nonveteran patients are admitted for study, and the branch provides oncology consultation for the VA Hospital (40 new consults per month).

Clinical associates rotate between the WVAMC and the Clinical Center in Bethesda so that exposure to a wider range of patients is achieved. Radiation therapy is provided by the Radiation Oncology Branch at the Clinical Center for oncology patients being treated at the WVAMC.

Laboratory investigations in human tumor cell biology involve studies of cell differentiation and culture, somatic cell hybridization, human tumor cell genetics and cloning of specialized products such as antibodies in hybrid cells. *In vitro* models for chemotherapy are under study and clinical investigation of tumor cell

kinetics is carried out. The program is designed to include clinical training in oncology and hematology and research experience either in the laboratory or in the conduct of clinical trials, depending on the individual's interests and goals. To further this end, close ties and collaboration with the Clinical Center in Bethesda are maintained.

Pediatric Oncology Branch—Dr. Arthur S. Levine

The Pediatric Oncology Branch conducts clinical and laboratory research activities related to the acute leukemias, non-Hodgkin's malignant lymphomas (especially Burkitt's lymphoma), soft-tissue sarcomas, osteogenic sarcoma, Ewing's sarcoma, neuroblastoma, aplastic anemia, cyclic neutropenia, and histiocytosis. Children, adolescents, and young adults are accepted for treatment, with the average age being 20 years. Three areas of clinical investigations are stressed: intensive chemotherapy and immunotherapy; hematologic support and bone marrow transplantation; and diagnostic and preventive techniques applicable to the infectious complications of the compromised host. The first-year program involves primary patient care responsibility with emphasis on management techniques of these areas of investigation. The clinical service is comprised of approximately 30 inpatient beds and an extensive outpatient department. The branch is particularly interested in the psychosocial aspects of cancer, and training in this area is emphasized. The branch also has an extremely active teaching program, with 12 weekly clinical and laboratory conferences and seminars. Candidates with prior training in internal medicine or in pediatrics may apply to this branch, and are eligible for Board certification in medical oncology or pediatric hematology-oncology.

Specific therapies in the neoplasms studied are designed to effect maximal reduction of the malignant cell population by chemical, surgical, and radiotherapeutic means, followed by experimental manipulations to prolong remission.

Comprehensive immunological assays are performed to assess the natural history of these diseases and the influence of treatment.

Transfusion and support studies explore the physiologic replacement of granulocytes and platelets in patients with compromised bone marrow function. A major area of interest is hematologic reconstitution through autologous bone marrow and stem cell transplantation.

In the infectious disease program, diagnostic and preventive maneuvers are designed to reduce the significant morbidity and mortality of infectious complications in the compromised patient. These maneuvers include the use of laminar-air-flow isolation and prophylactic antimicrobial agents.

In the second year of this program, clinical research training is offered in the areas previously described. In addition to clinical research, the branch has a strong program in basic laboratory investigation with emphasis on the molecular biology of tumor viruses, tumor cell biology, molecular and clinical pharmacology, tumor immunology, somatic cell genetics (using the cell hybrid technique), and immunohematology.

Opportunities for scholarly training in other areas of basic research can be arranged for selected candidates by utilizing excellent collaborative relations with other branches of the NIH.

Radiation Oncology Branch—Dr. Eli Glatstein

This branch offers a new training program for individuals who have at least 3 and preferably 4 years of postgraduate training. The program emphasizes combined modality approaches in the treatment of selected neoplasms, including small cell undifferentiated carcinoma of the lung, non-Hodgkin's lymphoma, carcino-

mas of the esophagus, breast, cervix, and pancreas, soft tissue sarcomas, malignant gliomas of the brain and various pediatric malignancies. Additional experience in the management of a wider spectrum of malignancies is gained through collaborative studies with the other branches of the NCI. There is continuous outpatient care of selected patients in order to ensure the opportunity for longitudinal observation and management. Laboratory investigation as well as clinical research is strongly encouraged. Facilities for *in vivo* and *in vitro* work are available. Investigation in cell biology as altered by irradiation, chemicals, and heat is also being carried out.

A newer emphasis is on investigational studies utilizing both irradiation and hypoxic cell sensitizers, hyperthermia, new combinations of cytotoxic agents, total body irradiation and various fractionation regimens in "radio-resistant" neoplasms. Rotations through the Medicine Branch, Surgery Branch, Pediatric Oncology Branch, Tumor Pathology and the Immunology Branch are available.

Surgery Branch—Dr. Steven A. Rosenberg

This branch, a surgical oncology unit, emphasizes a combined modality approach to the treatment of solid tumors and a broad program of laboratory research in cancer. A wide variety of malignancies are seen including melanomas, sarcomas, rectal cancers and pancreatic cancers. The Surgery Branch is committed to combined modality treatment and is investigating the use of adjuvant chemotherapy and immunotherapy, as well as the development of new surgical techniques. Laboratory efforts are closely related to clinical activities, and major laboratory programs in tumor immunology and surgical metabolism are in progress. The branch holds two clinical review and teaching sessions each week in which problem patients and preoperative patients are discussed in detail. Daily rounds, X-ray conferences, research seminars, and pathology seminars round out the surgical oncology teaching program. The Surgery Branch physicians also serve as general surgeons to the entire NIH and see a variety of general surgical consultations not related to the field of cancer.

Environmental Epidemiology Branch—Dr. Joseph F. Fraumeni, Jr.

The Environmental Epidemiology Branch, in the Division of Cancer Cause and Prevention, combines a program of clinical oncology with etiologic research. Clinical associates, appointed for 2 years, spend their first year in the Medicine Branch as primary-care physicians while their second year is devoted to epidemiologic and etiologic research. Studies are undertaken to clarify the risk of cancer among persons exposed to occupational, iatrogenic, or other environmental hazards and among persons with genetic or immunologic predisposition. Physicians selected for this program need not have specific training in epidemiology or genetics, but should be alert to etiologic clues derived from clinical observations. In studies of high-risk groups, including cancer-prone families, the associates are encouraged to collaborate with laboratory investigators in an effort to elucidate mechanisms of cancer susceptibility.

Associates may participate in a wide variety of epidemiologic investigations in the Branch, and gain experience in the techniques of epidemiology. Bimonthly seminars are held to discuss ongoing projects.

Also available in the Branch are 2-year research associate positions, which do not include the first year of patient care experience.

Developmental Therapeutics Program—Dr. Vincent T. Oliverio, Associate Director

This program is a broadly based endeavor which promotes and supports all pertinent activities essential to preclinical development of new treatment modalities for cancer, particularly chemotherapy. A systematic search is conducted for potential antitumor agents. These are subjected to programmed preclinical evaluation according to a scheme called the Linear Array. In this approach the program is responsible for all preclinical phases of development including acquisition and synthesis of materials, isolation and production of diverse natural products, screening, pharmaceutical development, toxicology, and pharmacology.

The Office of the Associate Director is responsible for overall administration of a large intramural research program and an extramural program on preclinical development of therapeutic modalities.

Clinical Associates

Each year about five individuals are recruited to fill positions as clinical associates.

Clinical associates are assigned to one of the laboratories on the program. Associates will be expected to perform independent and program-related research during their time in the laboratory. However, the program has been modified so that an associate, with approval of the preceptor, can make adjustments in assignments. This provides greater flexibility in choosing an assignment which most closely parallels the associate's immediate interests.

Some qualified clinical associates and research associates are selected to continue research for a third year and are assigned to a program-related research project.

Laboratory of Chemical Pharmacology—Dr. Richard H. Adamson

This laboratory brings together scientists who play an important role in the use of pharmacological information—plasma levels, tissue levels, mechanism of action, transport and metabolism studies—for experimental chemotherapy and earlier development and use of cancer chemotherapeutic agents for the clinic.

The pharmacologic properties of potential and established antitumor agents are evaluated *in vitro*, in animals and humans. These studies include evaluation of the antitumor activity of single agents, adjuvant and combination chemotherapy, and other modalities for cancer therapy. Other studies involve investigations on mechanism of action, structure-activity relationships, transport, dose-response relationships, effects on the immune system, mutagenic and carcinogenic potential of antitumor agents, and their disposition in laboratory animals and humans. The latter studies include the establishment of rates and rate constants which govern the passage of drugs from one body compartment to another.

Laboratory of Medicinal Chemistry and Biology—Dr. David G. Johns

This laboratory conducts an integrated program on the development of antitumor agents. Compounds with potential antitumor activity are synthesized and effects of such agents are assessed in experimental tumor systems *in vitro* and *in vivo*, and on a variety of potential subcellular target sites, *e.g.*, nucleic acids, nuclear proteins, microtubular protein, and en-

zyme systems. Analytical methodology for *in vivo* studies with new agents are developed and, where warranted, biological studies with these agents are extended to the preclinical and phase I stages. A contract-supported program to characterize the mode of action of new antitumor agents is also managed here. This laboratory stresses rapid and continuous utilization of the data generated from biological studies for elucidation of structure-activity correlations for guidance in synthesis of new antitumor agents of potential clinical value.

- Drug Design and Chemistry Section—Dr. John S. Driscoll

This section is involved in chemical research on the design and synthesis of new drugs for the treatment of cancer; the chemistry of therapeutic agents and drugs; the structure, purity, decomposition products and metabolites of antitumor drugs by analytical instrumental techniques; the development of structure-activity techniques to summarize existing data and provide guidelines for analog synthesis; and the promotion of an interdisciplinary approach to the synthesis and evaluation of rationally designated drugs by collaboration between chemical and biological scientists.

- Molecular Biology and Methods Development Section—Dr. Marco Rabinovitz

This section is developing approaches for the potentiation of cancer chemotherapeutic activities. Nutritional and pharmacological regimens are first explored in tissue culture and then extended to the tumor-bearing animal in attempts to direct cytotoxic agents toward the tumor cell and away from sensitive normal tissues. Synthesis of new cytotoxic and potentiating agents are also undertaken to achieve this goal. Biochemical studies include analysis of inhibition kinetics of binding, transport, and detoxification of cytotoxic agents in sensitive and resistant tumor cells and sensitive host tissues.

- Applied Pharmacology Section—Drs. Robert I. Glazer and David G. Johns

This section is studying the action of anticancer drugs on neoplastic cells at the molecular level. Included are investigations of the drugs' effects on the synthesis and post-transcriptional processing of nuclear RNA, the *in vitro* translation of messenger RNA, and the function of non-histone chromosomal proteins upon transcription. Characterization of target enzymes for anticancer agents is also pursued, using analytical techniques such as affinity chromatography, electrophoresis and isolectric focusing.

Laboratory of Molecular Pharmacology—Dr. Kurt W. Kohn

Mechanisms of action of anticancer agents are studied in culture and subcellular systems with particular attention to effects involving DNA and nuclear proteins. These investigations focus on the relation between drug-induced macromolecular damage (and its repair) and cell survival. Secondly, drugs are used as probes of the structure and function of DNA and chromatin. Experimental approaches include cell culture, DNA macromolecular damage measurements, and nuclear protein fractionation techniques.

Laboratory of Tumor Cell Biology—Dr. Robert C. Gallo

This laboratory's work is directed towards gaining a better understanding of the processes involved in the molecular control of cellular growth and differentiation, neoplastic transformation, and the pathogenesis of hematopoietic neoplasias, especially the myeloid leukemias. The ultimate goal is to develop new and improved approaches for therapy of human malignancies. Intimately related to this program is the search for and development of markers of neoplastic growth which give a quantitative as-

sessment of residual tumor cells after therapy.

These objectives have been pursued primarily in studies of the purification and properties of enzymes of nucleic acid biosynthesis, particularly the DNA polymerases (DNA-dependent and RNA-dependent) of human normal and leukemic cells and of RNA oncogenic viruses; the biochemical and biological properties of RNA tumor viruses; the origin and oncogenic potential of tumor viruses; human leukocyte growth and differentiation *in vitro* using various tissue culture techniques and identification, isolation and characterization of specific physiological factors which affect their growth and differentiation; mechanism(s) of the initiation of DNA synthesis in normal and tumor cells and the development of selective DNA polymerase inhibitors which are evaluated in human normal and leukemic cells; and immunochemical techniques for detecting reverse transcriptase in intact cells and other techniques for detection of viral-specific nucleic acids in intact cells and cloning of virus specific nucleic acid sequences. These studies are pursued with both animal and human leukemias.

Drug Evaluation Branch—Dr. John M. Venditti

Branch objectives focus on the discovery and preclinical development of new and improved therapies against cancer. This is achieved by *de novo* screening of synthetic and natural products for biological activities indicative of clinical utility; testing and evaluation of antitumor drugs for usage which may enhance therapeutic efficacy including modifications of treatment regimen; research on improved methods for drug evaluation; and developing and maintaining the resources needed to carry out the program.

The Office of the Chief implements, establishes, and maintains contract-based projects aimed at improving combination chemotherapy and studying related problems of resistance, cross-resistance, and drug interactions; and at improving combined treatment modalities, including chemotherapy combined with radiation or surgery. End results and recommendations of new therapies for development to clinical trial are presented to DCT staff via reports, to decision groups and the scientific community via formal publication.

- Automated Information Section —John F. Waters

Principal responsibilities of this section are managing the biological data processing system for the Drug Evaluation Branch, providing resources for automated processing storage, and retrieval of biological data generated in contract antitumor testing laboratories. The staff generates data processing programs which are maintained and operated by contractual arrangements with qualified organizations. The biological data base can be queried to provide information on antitumor activity of tested materials. The system provides information for evaluation of screening models, design of new test systems, review of compounds being considered for clinical trial, and providing statistical information required for effective program management.

- Mammalian Genetics and Animal Production Section—Dr. Joseph Mayo

The primary function of this section is to provide healthy laboratory animals with defined genetic characteristics to contract testing laboratories and to other intramural and extramural laboratories. Specifically, the section establishes and manages contracts with primary genetic centers, rodent production centers, disease diagnostic laboratories, host-tumor histocompatibility laboratories, and organizations concerned with laboratory animal care.

- Screening Section—Betty Abbott

Emphasis is placed on large-scale screening of synthetic and natural products in rodents bearing transplantable tumors of both animal and

human origin. The worldwide program is conducted through contracts with qualified institutions. Staff establishes and manages contract laboratory projects, monitors scientific and technical sufficiency, reviews results, selects materials worthy of further study at the preclinical level, and recommends new agents for development to clinical trials against cancer. Where appropriate, *in vitro* screens are used for the bioassay of natural product fractions leading to isolation of the antitumor active component. The Screening Section selects animal-tumor models for use as screens and establishes parameters and criteria for antitumor activity.

Drug Synthesis and Chemistry Branch—Dr. Ven L. Narayanan

The branch is the primary source for procuring new chemicals and drugs via selective acquisitions and chemical syntheses and serves as liaison with the scientific community submitting compounds for biological evaluations. Materials are received from industrial, governmental, academic, and research institutions, both domestic and foreign. A chemical compound bank is maintained for storage and shipping materials. A Chemical Information Program on materials submitted and distributed is also maintained. Structure-activity relationships and compound preselection methodology development are of prime concern to the branch.

The processing, custody, and compliance of all "Commercial Discreet Agreements" for submitting chemical compounds to the National Cancer Institute from worldwide industrial organizations is also a branch function.

- Drug Synthesis Section—Dr. Ven L. Narayanan

Activities are directed toward the design and synthesis of unique chemical compounds as potential anticancer agents. The section manages a contract synthesis program for the development of new drugs for the biological screen. New leads for drug design and structural modification are revealed through structure-activity studies and biochemical, toxicological, and clinical rationale.

- Chemical and Drug Information Section—Dr. Ven L. Narayanan

The automated chemical information system is operated to support the acquisition and distribution of chemicals and drugs acquired for antitumor screening and to store and retrieve chemical information. Methods are developed for compound preselection for screening. Structure-activity studies are made to optimize acquisitions by identifying chemical classes to be de-emphasized because they are largely negative or adequately studied and to develop statistical models to predict the activity of potential acquisitions. Computer searches are made to identify new or duplicate compounds in the programs, as well as substructure searches. A chemical data base is maintained on compounds of interest to the National Cancer Institute.

Natural Products Branch—Dr. John D. Douros

The branch is engaged in the development of more effective natural product agents for human cancer chemotherapy, primarily through contract-supported projects. It supervises worldwide procurement of natural products, evaluates these agents, and prepares large amounts of the active agent. Quality control in the preparation of the material and expediting the drug to a stage for toxicological evaluation are also part of the branch's responsibility. The active natural products are modified by chemical and biological transformation to increase therapeutic effectiveness and solubility.

Research efforts are directed toward obtaining new natural products through various techniques, precursor feeding, continuous fermentation, production of antineoplastic agents in cell culture, and systemic evaluation of microbes (thermophiles, specific genera). Older compounds in the pro-

gram are thoroughly reviewed and tested with new *in vivo* and biochemical screens. The branch evaluates new prescreens and initiates biochemical studies on natural products as early as possible in the program. Biological modifiers such as interferon are also obtained for the program.

• Plant and Animal Products Section—Dr. Matthew Suffness

This section monitors contracts on plant and animal development of antineoplastic agents. It determines new areas of plant and animal research which might yield new drugs and also ensures a supply of drugs of interest.

• Fermentation Section—Amelia M. Acierto

This section monitors contracts in the area of fermentation development of antineoplastic agents. It determines areas of research, such as microbial genetics, biotransformation, feedback repression, and isolation of unusual organisms which yield new anticancer drugs. The section also monitors process development of compounds so that clinical trials will have sufficient material for thorough evaluation.

Pharmaceutical Resources Branch—J. Paul Davignon

The branch provides comprehensive pharmaceutical services to the Division of Cancer Treatment through a major contract-supported program. The contract support areas include: chemical preparation laboratories, chemical pilot plant production, analytical services, product research and development, and pharmaceutical manufacturing. A laboratory of formulation development is also maintained and managed by the branch to develop dosage forms of high interest.

• Chemical Resources Section—Dr. Robert R. Engle

This section provides for resynthesis, large-scale production, and procurement of chemical substances. It also provides, through contract support, the preparation of radiolabeled materials. All materials are required to be of the highest quality and to meet strict product specifications.

• Analytical and Product Development Section—James C. Cradock

This section provides quality assurance for chemical and formulated products used in the Division of Cancer Treatment. It also supports a drug formulation laboratory for development of suitable pharmaceutical dosage forms for clinical trial. Since most preparations are intended for intravenous use, studies are undertaken to assess the solubility and stability of investigational drug substances in various pharmaceutical vehicles. New approaches to enhance solubility are emphasized since few suitable methods are available to the formulator of parenteral products.

• Clinical Products Section—Larry M. Kleinman

This section provides, through contract support, for the large-scale production of investigational dosage forms suitable for human use. It also provides, through procurement mechanisms, for commercially available dosage forms to be used in clinical trials. In addition, this section is responsible for the storage and distribution of these antitumor agents to investigators throughout the world. It also monitors and directs a computerized drug information system. Pharmaceutical data are assembled in support of the Division of Cancer Treatment's Investigational New Drug Applications.

Toxicology Branch—

This branch organizes, plans, directs, manages, and evaluates an extramural contract program to investigate and describe the qualitative and quantitative toxicities of potential antitumor agents and modalities in experimental animals. Research guidance is provided for the development of organ specific toxicity assays and for investigations on the toxicity of second generation analogs. Toxicological assessments are contributed to

the preparation of Investigational New Drug Applications before their submission to the FDA and initiation of Phase I clinical trials. The branch conducts continuous surveillance of the literature for new developments in the field of toxicological evaluation of synthetic and natural products which may be applicable to the needs of the Developmental Therapeutics Program and the Biological Response Modifiers Program.

Baltimore Cancer Research Program (BCRP)—
Dr. Peter H. Wiernik
Acting Associate Director

The Baltimore Cancer Research Program, located at the University of Maryland School of Medicine and Hospital in Baltimore, Maryland, is an intramural program of the NCI which conducts both clinical and laboratory research into cancer therapy. Treatment of adult patients with leukemia, lymphoma and advanced metastatic carcinomas and sarcomas is emphasized. Multimodality therapeutic trials, intensive supportive care programs, pharmacokinetic and pharmacodynamic drug evaluations, tumor assay systems and basic enzymologic and immunologic studies are integrated into a unified program aimed at improving cancer treatment. This collaborative endeavor between the National Cancer Institute and the University of Maryland School of Medicine and Hospital provides the community with a Referral Oncology Treatment Program.

Clinical Oncology Branch—
Dr. Peter H. Wiernik

This branch conducts a clinically oriented therapeutic research program in support of the Division of Cancer Treatment. Inpatient facilities include 36 beds, 4 intensive care beds, and 4 laminar air flow isolation beds plus an extensive outpatient facility along with the necessary support services including pharmacy, hematology and microbiology laboratories, cell support laboratory, social worker, psychiatrist, medical records and computer services. This unit, contained on one floor of the hospital, provides a close-knit program for continuity of care. Although most treatment protocols are locally developed, the BCRP is a contributing member to Cancer and Leukemia Group B. Patient care is also aided by a computerized Problem-Oriented Medical Information System (PROMIS) with the potential of retrieval and analysis of cancer research treatment data. Combined modality therapy and immunotherapy studies have been initiated. In addition, the BCRP provides consultation to the University of Maryland Hospital, the Baltimore VA Hospital and the greater Baltimore medical community. Approximately 5 clinical associates are chosen each year. Minimal requirements are 2 but preferably 3 years of postgraduate training. The initial year consists of primary care responsibility with extensive teaching programs in clinical oncology. During the first year, associates determine, in consultation, their choice of research activities in the subsequent year. Superior associates are invited to remain for a third year of training.

- Medical Oncology Section—
Dr. Joseph Aisner

This section is engaged in Phase I and II studies of new experimental antineoplastic drugs. Phase III and combined modality studies are conducted in patients with breast, lung, and gastrointestinal cancer as well as in patients with metastatic renal adenocarcinoma. In addition, studies of whole body hyperthermia as an adjuvant to the drug treatment of cancer patients is under investigation.

- Infection Research Section—
Dr. Stephen C. Schimpff

This section plans and conducts research into the epidemiology and predisposing factors to infection, the mechanisms of infection development and progression, infection prevention including laminar air flow room isolation and alimentary canal microbial suppression and the diagnosis and

treatment of proven and suspected infection in patients with cancer.

• Microbiology Section—Dr. Viola Mae Young

This Section maintains the clinical microbiology laboratory for patient care support and conducts research on microbial surveillance of the patient and his or her environment, characterization of new organisms, and evaluation of new antimicrobial agents.

• Cell Component Therapy Section—Dr. Charles A. Schiffer

This section is responsible for providing platelet and granulocyte transfusion therapy, investigating new methods of platelet, granulocyte, lymphocyte and blast collection, cryopreservation and storage, and studying histocompatibility testing for blood cell component transfusion.

• Clinical Research Pharmacy Section—Mr. Clarence L. Fortner

This section provides a complete pharmacy service including drug preparation, pharmaceutical informational input and detailed drug monitoring including patient-drug histories, drug-related toxicities along with complete records of both investigational chemotherapeutic and supportive care drugs plus standard drugs used for the treatment of oncology patients.

Laboratory of Clinical Biochemistry—Dr. Nicholas Bachur

The laboratory is researching problems of clinical importance through the disciplines of cellular biology, biochemistry, physiology, and pharmacology. Emphasis is placed on approaches that integrate basic and clinical sciences. The laboratory studies endogenous factors that regulate cellular growth and differentiation, mechanisms of cellular blastogenesis, involvement of cellular membranes in differentiation and cellular recognition, and chemical control of cellular growth and differentiation. Mammalian materials often are correlated with clinical studies. Laboratory expertise is in cellular biology and ultrastructure, cellular biochemistry, enzymology, biochemical and clinical pharmacology, and in analytical technology.

Laboratory of Molecular Biology—Dr. Carl Levy

This group examines, at the molecular level, the regulatory pressures to which a cell is subjected during the course of its development. Through sophisticated techniques in immunology and enzymology, critical evaluation is made of factors within the cell that may cause deviation from normal development. Emphasis is placed on such factors as enzyme constituents in neoplastic disorders, and specific changes of cellular constituents as indicators of the presence of neoplastic disease. The laboratory investigates the means by which the measurement of human immune responsiveness can be improved and extended. Another vital concern of the laboratory is the development of specific tumor cell marker systems.

NCI Informational Bulletin

Prospective applicants to the National Cancer Institute may obtain an NCI Informational Bulletin by writing Dr. Alan Rabson, Director, DCBD, NCI, Building 31, Room 3A03, National Institutes of Health, Bethesda, MD 20205.

National Eye Institute

Carl Kupfer, M.D.,
Director
Elmer J. Ballintine, M.D.,
Clinical Director

Clinical and Research Associates

The National Eye Institute conducts and supports research on the cause, natural history, prevention, diagnosis, and treatment of disorders of the eye and visual system.

The Institute selects three clinical associates from those candidates who have completed an accredited 3-year ophthalmology program. Clinical associates spend time in both clinical and laboratory research including patient care activities.

In selection of clinical and research associates, preference will be given to those who will continue their research training either at the National Institutes of Health or in an academic setting elsewhere with an eventual career in full-time clinical or laboratory research.

The National Eye Institute has developed its clinical and research program into four major branches, the Laboratory of Vision Research, the Laboratory of Sensorimotor Research, the Office of Biometry and Epidemiology, and the Clinical Branch.

Office of Biometry and Epidemiology—Fred Ederer

The Office of Biometry and Epidemiology conducts studies that tend to fall into the broad areas of clinical trials and natural history, on the one hand, and epidemiology on the other.

The clinical trials section is now responsible for three national multiclinic trials involving vitrectomy, drugs, and photocoagulation, as treatments to prevent progression in patients with diabetic retinopathy. These studies include thousands of patients, and combine the skills of several disciplines, including clinical, statistical and computer sciences. Data generated in these studies not only provide a base for treatment strategies, but permit investigation of the extent to which risk factors other than treatment are related to disease progression.

The epidemiology section generates data on the prevalence, incidence and distribution of diseases of the eye. Such data are used to evaluate hypotheses on the causes of such diseases. Data sets from the Framingham Eye Study and the Health and Nutrition Examination Survey are being actively analyzed to explicate the risk factors for changes in the lens and retina. A major study of the antecedents of cataract is in an early stage of planning.

Laboratory of Vision Research—Dr. Jin Kinoshita

The laboratory is engaged in research involving the following disciplines:

Biochemistry—This section conducts studies on the chemistry and metabolism of the lens and cornea, with particular emphasis on the formation and prevention of sugar cataracts in experimental animals. The physical chemistry of model gel systems, structural and functional aspects of the bovine rhodopsin molecule, protein synthesis in the retina, biochemistry of visual pigments, biochemistry of the pigment epithelium, and the metabolism of photoreceptors are also under investigation. In addition, synthesis of sugar-containing polymers in the retina are being stud-

ied to determine what role sugars play in the transport and assembly of rhodopsin into disc membranes.

Experimental Embryology—This section identifies and characterizes the myriad tissue interactions that control orderly growth of the vertebrate eye and assure that each ocular part develops a size, shape, and orientation appropriate to its function in this sense organ. Because most congenital defects of the eye are attributable to interference with these interactions, identification and characterization is considered indispensable to establishing the etiology of most congenital eye defects. Researchers are determining which tissues are responsive to such influences, the duration of these potencies and competencies during embryogenesis, the specificities of these interactions, and the nature of interactions which control morphogenesis.

Particular attention is being focused on newly discovered, cell-free, collagen containing "initiator layers" which are transiently produced by several epithelia of the embryonic eye and thought to be directly involved in the differentiation and morphogenesis of most organs of the body.

Experimental Pathology—Research being conducted in this section centers on anatomic and pathologic studies of ocular tissue. Studies of the effects of intraocular pressure on eye tissue, the damaging effect of light on the retina, laser effects on the retinal blood vessels, and the pathology of glaucoma are among current projects.

Neurophysiology—Investigations on the cellular organization underlying visual perception are currently underway in this section. Studies are being conducted on the responses of single nerve cells at various levels in the visual nervous system of mammals. The purpose of this work is to understand how nerve cells contribute to visual sensations such as color, shape, movement and depth. The technique employs fine microelectrodes which can be inserted into the brain in order to record from single nerve cells. It uses refined optical methods to enable an experimenter to stimulate the retina with spots or slits of colored lights whose movement and shape can be quantitatively controlled. It involves electrophorescing dye into single cells whose responses have been studied and then finding these cells within the brain or retina.

By this means both structure and function of nerve cells can be correlated and the underlying circuitry of the visual system understood. This approach requires close interaction between single cell physiology and cellular anatomy at the light and electronmicroscopic level.

Retinal and Corneal Metabolism—This section is investigating the function of the retina, pigment epithelium, and cornea in relation to clinical diseases such as retinitis pigmentosa and keratomalacia.

The mechanism by which visual cells detect light and produce neural messages is not known. Calcium may play a role in the process since it mimics the effects of light on the retina and is found in very high concentrations in pigment epithelium and retinal photoreceptors. Small intracellular messengers called cyclic nucleotides have also been found in extraordinarily high concentrations in retinal photoreceptors. Since light markedly affects their concentration they, too, are probably intimately involved in the visual process. A method of injecting various substances into visual cells is now being developed to determine directly the effect of these substances on the visual process in both normal and pathologic conditions.

Studies on the synthesis and degradation of the visual protein rhodopsin have helped explain how retinal photoreceptors are renewed. Defects in this process may underlie some

forms of retinal degeneration; thus, studies using dystrophic retinas of test animals are underway to compare the process of photoreceptor renewal in normal and pathologic conditions. Substances such as hormones and neurotransmitters which affect the normal growth and development of retinal cells in tissue culture are being assessed. Several have already been identified and are being further studied in relation to their role in retinal function.

Specific receptor molecules for vitamin A have been found in retina and pigment epithelium. These receptors are probably involved in the normal uptake, distribution and retention of the vitamin in the visual system. Differences in receptor concentrations in retinas of normal humans and patients with retinitis pigmentosa have been found.

Vitamin A receptors are also present in the cornea and conjunctiva. The possible relationship of these receptors to corneal disease is being considered. Other aspects of corneal physiology, such as glutathione metabolism, are under investigation. Such studies are important not only for understanding corneal function and transparency but for improving corneal transplant and surgery techniques as well.

Laboratory of Sensorimotor Research—Dr. Robert Wurtz

This laboratory conducts research on the central neural bases of vision and eye movements in the primate, and the application of these results to clinical problems in patients with visuomotor deficits. The laboratory uses a multidisciplinary approach, availing itself of techniques of neurophysiology, neuroanatomy, experimental psychology, psychophysics, systems engineering, and computer science.

One series of projects is designed to elucidate the central neural mechanisms in the control of visually guided eye movements. The activity of single neurons in cortical and subcortical areas is recorded using microelectrodes placed in the brains of behaving animals, in order to analyze the relationship of neural events to eye movements and the presentation of visual stimuli. Quantitative studies of eye movement are performed in animals with lesions in those brain areas which physiological recordings have indicated may be important in the neural mechanisms underlying eye movement and visual perception. The anatomic connections of these areas of interest are studied using axoplasmic transport methods.

A second series of experiments investigates the visual processing underlying visual perception. These experiments correlate the discharge of single cells within cortical and subcortical regions of the brain with the stimulus presented to the monkey.

In another series of studies the vestibulo-ocular system is used as a tool to study the mechanisms by which the brain can adjust to environmental changes. This adaptive plasticity is studied using systems analysis of single neuron discharge patterns recorded from performing animals, and analysis of the performance of monkeys, normal human subjects, and patients with oculomotor deficits.

The ability of patients with visuomotor deficits is studied using paradigms for performance that have been developed using normal humans and monkeys, in order to study residual abilities following damage to discrete brain areas, and to develop strategies for rehabilitation of brain damaged patients.

Since recent advances in sensorimotor physiology and psychophysics have been made possible by developments in the application of the on-line laboratory computer to these problems, a significant effort in the laboratory is the development and refinement of computer methods for the control and analysis of experimental results.

Clinical Branch—Dr. Elmer J. Ballintine

The branch plans and conducts clinical research into the causes, prevention, diagnosis, and treatment of visual system disorders. It translates laboratory research results into clinical application, directs and administers the Institute's clinical care program, and assures functioning of the eye ward and clinic in the NIH Clinical Center.

It is the branch's responsibility to investigate the causes and prevention of visual impairment. The major areas under study are:

- Cataracts of unusual origin and congenital cataracts are being studied in clinical, biochemical, histochemical, and histopathologic correlative research projects.
- Neuro-ophthalmology: Patients from the ophthalmic and neurologic services are being studied using advanced methods for electro-oculography, pupillometry, video tape recording, and computer analysis. The main emphasis of these studies is on cerebellar disorders that affect ocular movements.
- Glaucoma: Intraocular fluid dynamics in normal and glaucomatous eyes and their alteration by pharmacologic agents are being studied. A controlled clinical trial to test the value of early treatment of ocular hypertension is underway. Innovative surgical techniques are being assessed in selected cases of primary, secondary, and congenital glaucoma and in cases in which antiglaucoma surgery has failed. The properties of trabecular meshwork are being studied in tissue culture.
- Ophthalmic genetic studies include clinical, biochemical, and electrophysiologic studies of hereditary retinal diseases. While previous research efforts have been confined to areas of diagnosis, classification, and family studies, current investigations are expected to provide a better understanding of the pathogenesis of the diseases. The night blindness syndromes, familial vascular retinopathies, familial macular disease, and color deficiency are of particular interest.

The pathogenesis of unusual types of congenital or developmental anomalies of the eye is being studied under protocol. These cases include pigment dispersion syndrome, progressive essential iris atrophy, oculocutaneous albinism and abnormalities of the anterior chamber angle associated with glaucoma.

- Retinal deteriorations: Clinical, biochemical, cell biological and metabolic investigations are being conducted to define underlying mechanisms in diseases such as senile macular and related degenerations and the maculopathy of retinitis pigmentosa. Macular edema is also of special interest.
- Vascular diseases: Clinical investigations are being conducted in the treatment and underlying mechanisms of diabetic retinopathy.
- Ocular connective tissues: Characterization and purification of extracellular matrix molecules synthesized by normal and abnormal ocular tissues, immunofluorescent antibody studies, and the enzymology and immunology of corneal melting are being investigated actively.
- Ophthalmic pathology: Eyes obtained from autopsies or enucleations performed at the Clinical Center are processed and studied histopathologically and electronmicroscopically. Many of these eyes are from subjects who have rare or unusual metabolic diseases or who have been subjected to prolonged courses of anticancer treatment. There is opportunity for close collaboration with investigators in the Laboratory for Vision Research in the Institute.
- Ocular immunology: Immunologic mechanisms relating to ocular inflammatory disease are being studied. The possible role of ocular autoimmunity in uveitis is being actively investigated. Patients with posterior uveitis, i.e. toxoplasmosis, pars plani-

tis, birdshot choroidopathy, and sarcoid are being sought in order to evaluate their immunologic responses. The evaluation of patients with ocular inflammatory disease also includes monitoring their ocular physiologic responses during disease and when the inflammation is quiescent. The relationship of HLA and the immunologic response of ocular inflammatory patients to antigens is being looked at, as are other immunologic factors, such as antibody production, suppressor cell activity and macrophage responsiveness. Patients are in addition being sought for a controlled double masked study in the therapy of ocular toxoplasmosis.

National Heart, Lung and Blood Institute

Robert I. Levy, M.D.,
Director
Jack Orloff, M.D.,
Director of Intramural Research
Harry R. Keiser, M.D.,
Clinical Director

Candidates for research and clinical associate positions have only one interview in this Institute. Associates are interviewed by a committee made up of the director of intramural research, the clinical director, and the deputy clinical director. Candidates are selected without regard to their specific research interests so long as their interest is represented in one of the numerous laboratories and branches of the National Heart, Lung, and Blood Institute (NHLBI). After appointment and prior to entering on duty each appointee will have an opportunity to select the laboratory in which to work. The choice is based on the background and interests of the associate and appointment to the chosen laboratory is contingent on the ability of that particular laboratory to furnish proper supervision and facilities. On the basis of past experience, it appears virtually certain that each associate will be able to work with the group of his or her choice. The level of research responsibility and freedom will depend upon the associate's training and experience as well as desires.

Each associate in medicine will devote time primarily to research in the laboratory under the supervision of a preceptor in the area of selection. Each is expected to engage in appropriate course work in the basic, medical, and allied sciences as well as tutorial seminars, and to take an active part in the journal club and other exercises of the laboratory.

All appointments as clinical and research associates are for a minimum of 2 years with a third optional year. In the past, most clinical and research associates have elected to remain for 3 full years and have been accorded this privilege.

Clinical Associates

These appointments are designed to give physicians training in both clinical and basic research. Candidates must have satisfactorily completed a minimum of 2 years of residency training in general internal medicine in a program approved by the American Board of Internal Medicine by the starting date of their appointment. The first year of the clinical associateship will be credited as a third year of training in internal medicine by the American Board of Internal Medicine if the candidate's clinical competence was satisfactory

during the previous 2 years of training and is satisfactory here.

Clinical associates will be responsible, under the guidance of investigators on the NHLBI staff, for the primary medical care of research patients during 10 to 12 months of the first year of their service. During this time they will rotate through the four medical services that serve the clinically oriented branches of the Institute and assist in the work of the service with consultations and in the outpatient department. These services occupy 75 beds and include cardiology, hypertension-endocrinology, lung, and hematology and metabolism.

The clinical period is one of intensive training under direction of the clinical director and staff. It offers exposure to case material of extraordinary range and to highly sophisticated approaches to investigation of disease.

The clinical associate devotes both time off the wards and a full 12-14 months of the 2-year assignment to laboratory research under direction of a preceptor *in any one of the Institute laboratories, either clinical or nonclinical*. No clinical responsibilities are required during the second or the optional third year for associates who have chosen nonclinical laboratories.

Clinical Associates in Surgery

The Surgery Branch appoints four to five associates in surgery for a 2-year period beginning each July 1. The program is designed for young surgeons with primary interests in cardiovascular surgery and cardiovascular physiology. In making appointments, preference will be given to candidates contemplating a career in research or academic medicine. Candidates must have completed an internship and at least 1 year of surgical residency by the starting date of their appointment. Candidates interested in this possibility and desiring additional information are encouraged to write to Dr. Andrew G. Morrow, Chief, Surgery Branch, NHLBI, Bldg. 10, Room 6N252, NIH, Bethesda, MD 20205.

Research Associates

These appointments are designed to give highly qualified physicians an opportunity to do research in a basic laboratory under the direct supervision of an experienced preceptor. Usually physicians enter the appointment after completing internship and 1-year residency, but there are no specific requirements for postgraduate training after the M.D. degree. While no clinical assignments are involved the associates are welcome to attend any of the clinical teaching exercises.

Staff Associates

Laboratories with the NHLBI sometimes have openings for staff associates appointed from the matching program. When such appointments are available they are listed in the Program Area Selection Checklist for the Institute. Selections for those positions are made by the chief of the branch or laboratory. The position of staff associate is otherwise comparable to that of research associate.

Staff Associates in Epidemiology

The Epidemiology Branch conducts population-based studies on the occurrence and natural history of cardiovascular, cerebrovascular, blood and obstructive pulmonary diseases in general and selected populations in the United States and foreign countries. Through clinical examinations and analyses of available data, these studies seek to improve knowledge of the personal, environmental, and familial factors underlying these disorders. One or two candidates are chosen each year for 2-year assignments in Bethesda or for one of the field programs. The associateships may begin after internship or after 1 year of training in a clinical residency or school of public health. Interested candidates are encouraged to write to Dr. Manning Feinleib, Chief, Epidemiology Branch, NHLBI, Bethesda, MD 20205, for more detailed information about specific assignments.

Joint Endocrinology Training Program

Clinical associates from the NHLBI may participate in a 3-year joint Endocrinology Training Program. The aim of the program is to provide clinical and research experience in a wide variety of endocrine and metabolic diseases and to qualify associates for the Endocrinology Subspecialty Boards. NHLBI participants will spend an additional 6 months in full-time clinical activity consisting of 3-month rotations on the endocrine services of the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Institute of Child Health and Human Development. During this 6-month clinical period, the associate will function as a primary care physician for inpatients, see consultations, and participate in outpatient work, rounds, and seminars. The remainder of the associate's 3 years will be spent primarily in research activity within the NHLBI, although he or she will be expected to continue participation in outpatient work and rounds. In general, it will not be possible for more than two NHLBI associates to enter this program in any 1 year.

Formal Instruction

The major form of postgraduate instruction is through the evening courses offered by the Graduate Program of the Foundation for Advanced Education in the Sciences, Inc., and through the NIH tutorials. Clinical, research and staff associates are expected to take advantage of this academic work. (See part 4, page 111.)

Clinical Research Branches

Cardiology Branch—Dr. Stephen E. Epstein

- Section on Cardiovascular Diagnosis—Dr. Kenneth Kent

Investigations are oriented toward the diagnosis of acquired and congenital heart diseases, the evaluation of operative and nonoperative forms of treatment, and the elucidation of mechanisms responsible for the hemodynamic changes produced by heart failure.

- Section on Experimental Physiology and Pharmacology—Dr. Stephen E. Epstein

Research is aimed toward understanding the physiologic, anatomic, and biochemical mechanisms respon-

sible for control of the normal heart and circulation, elucidation of the alterations produced by ischemic and nonischemic heart disease, and evaluation of interventions designed to reverse the biochemical and, thereby, the physiologic aberrations of function. Several approaches are being employed to achieve the above, including hemodynamic, echocardiographic (one- and two-dimensional systems), and radionuclide studies in man, electronmicroscopic and biochemical studies of tissues obtained from human and animal surgical specimens and pharmacological investigations in man and animals.

- Section on Molecular Cardiology—Dr. Robert S. Adelstein

Current investigations are directed toward understanding the function and control of contractile proteins in muscle and nonmuscle cells. The role of cyclic nucleotides and myosin phosphorylation in regulating actin-myosin interaction is of particular interest. Projects include myosin phosphorylation and the regulation of kinases and phosphatases in smooth muscle, heart and nonmuscle cells such as brain, blood platelets and myoblasts.

Clinical Hematology Branch—Dr. Arthur W. Nienhuis

This branch applies the techniques of cell and molecular biology aimed toward understanding and treating human disorders of hemoglobin synthesis and erythroid differentiation. Major research areas include the cellular and molecular mechanisms of regulation of the individual globin genes during erythroid differentiation. Patients with a broad range of red blood cell diseases are studied on the clinical service. Intracellular factors which influence the binding of oxygen to hemoglobin are being explored, particularly as they pertain to the deoxygenation and intracellular gelation of sickle hemoglobin. The value of iron chelation therapy in patients with transfusional hemosiderosis is under investigation. Joint studies are also carried out with the Laboratory of Molecular Hematology.

Hypertension-Endocrine Branch—Dr. Harry R. Keiser

This branch represents a merger of the former Endocrinology and Experimental Therapeutics Branches. A major emphasis is on research related to hypertension; activities are wide-ranging, as indicated by the description of section activities.

- Section on Experimental Therapeutics—Dr. Harry R. Keiser

A wide spectrum of research opportunities is offered, ranging from basic biochemistry and pharmacology to the study of chemical factors in disease and clinical response to drugs. Major emphasis is on hypertension with studies of the kallikrein-kinin system, reninangiotensin-aldosterone system, prostaglandins and catecholamines and their interactions, conducted both in man and in experimental animals. Other studies encompass disorders of serotonin and histamine.

- Section on Biochemical Pharmacology—Dr. Walter M. Lovenberg

This section conducts a broad research program on the molecular mechanism of neuronal function. Studies relate primarily to the properties and regulation of enzymes responsible for the biosynthesis of neurohumoral amines. The role of these systems in disease states, particularly hypertension, is of prime interest, and investigations are extended from the molecular level to experimental animals and man.

Molecular Disease Branch—Dr. H. Bryan Brewer

The research activities of this branch are directed toward the elucidation of the molecular mechanisms involved in lipid transport and metabolism in normal individuals and patients with disorders of lipid metabolism and atherosclerosis. Studies take several approaches employing protein chemistry, immunology, tissue culture, and enzymology. Clinical

research is focused on the effects of drugs and therapeutic diets on dyslipoproteinemia and on kinetic analysis of the metabolic defects in patients with this disease. Activities are integrated in such a way that, if associates wish, they may participate in collaborative research involving several different areas.

Pathology Branch—Dr. William C. Roberts

This branch is concerned with the study of morphologic aspects of cardiovascular and pulmonary diseases and their correlation with functional derangements. Morphologic analyses include transmission and scanning electron microscopy.

Pulmonary Branch—Dr. Ronald G. Crystal

Research in this branch is designed to investigate the structure and function of the lung in health and disease through cellular and biochemical methods. Both laboratory and clinical investigations are conducted. Techniques of protein chemistry, molecular biology, tissue culture, and immunology are used. Emphasis is placed on the regulation of synthesis and degradation of connective tissue and on the inflammatory and immune processes in the normal and diseased lung. Clinical research is directed toward correlating physiologic, biochemical, immunologic, and morphologic observations in patients with interstitial lung disease, destructive lung disease, hereditary disorders of connective tissue, hypersensitivity lung disease, and other lung disorders with an immunologic basis.

Surgery Branch—Dr. Andrew G. Morrow (See page 37, Clinical Associates in Surgery.)

Basic Research Laboratories

• Section on Theoretical Biophysics—Dr. John L. Stephenson.

The primary interest of this section is the theory of transport processes in biological systems, with particular reference to problems in cardiovascular, renal, and membrane physiology. The section is concerned with the formulation of theoretical models and the development of mathematical and computational methods for their analysis. Currently, much of the research centers on the mechanism of urine formulation in the mammalian kidney and theoretical aspects of epithelial transport of electrolytes and water.

Laboratory of Biochemical Genetics—Dr. Marshall Nirenberg

• Section on Molecular Biology—Dr. Marshall Nirenberg

This section is primarily concerned with basic biochemical studies pertaining to the transfer of genetic and neural information, for example, genetic programs for differentiation that determine informational reactions of neurons. Systems and problems involve the culture of mammalian cells and hybrid cells. Studies are also done on gene function for informational molecules such as enzymes of transmitter metabolism receptors, membrane ionophores, cyclic nucleotides, and other components required for cell recognition and communication.

• Section on Macromolecules—Dr. Alan Peterkofsky

This section is concentrating on studies of cellular control mechanisms. One area of interest involves the hypothalamic tripeptide thyrotropin releasing factor. The biological properties of some new derivatives of thyrotropin releasing factor are under investigation. Another focus of attention is the control of the synthesis and metabolism of cyclic nucleotides in bacterial cells.

Laboratory of Biochemistry—Dr. Earl R. Stadtman.

• Section on Enzymes—Dr. Earl R. Stadtman

This group studies diverse enzyme

systems that offer unique opportunities to elucidate basic biochemical phenomena, namely, those concerned with vitamin-coenzyme function, the cellular regulation of metabolism, the energy-dependent transport of metabolites across membrane barriers, and mechanisms of enzyme action.

• Section on Intermediary Metabolism and Bioenergetics—Dr. Thressa C. Stadtman

This section is concerned primarily with investigations on the mechanisms of anaerobic amino acid dissimilation and phosphorylation coupled with anaerobic electron transfer processes. Special emphasis is on the roles of various coenzymes (vitamin B_{12}, coenzyme, CoA, pyridoxal phosphate, flavins, pyridine nucleotides, lipoic acid, and naphthoquinones) and of various electron transfer proteins, such as selenoproteins, ferridoxins, flavoproteins and sulfhydryl proteins.

• Section on Protein Chemistry—Dr. Ann Ginsburg

Studies on protein structure in this laboratory are directed toward understanding protein-ligand interactions, protein-protein interactions, and enzyme catalysis and regulation.

Laboratory of Cell Biology—Dr. Edward K. Korn.

This laboratory conducts research on the structural basis of the biochemical properties of protein molecules and on their integration into functional supramolecular structures. It also studies the molecular and ultrastructural aspects of cellular events.

• Section on Cellular Biochemistry and Ultrastructure—Dr. Edward D. Korn

This section studies structure-function relationships at molecular and cellular levels. Present activities are focused on the molecular and ultrastructural basis of cell motility. Cytoplasmic actin, myosin, and related proteins are purified from nonmuscle cells and their interactions studied and compared to their muscle counterparts. Currently, emphasis is on the regulation of action polymerization, the regulation of actin-activation of myosin-ATPase, and the characterization of multiple myosins in a single cell. Opportunities are available for research and training in biochemistry and electron-microscopy.

• Section on Cellular Physiology—Dr. Evan Eisenberg

This section conducts studies on the molecular events of muscle contraction including the interaction of actin and myosin with each other and with the control proteins, tropomyosin and the troponins. Emphasis is on kinetic studies with pure proteins.

• Section on Membrane Enzymology—Dr. Richard Hendler

This section studies enzyme systems that require organization on or interaction with membranes in order to ensure their proper functioning. The synthesis of DNA by enzyme complexes and the electron transport chain of *Escherichia coli* are presently being investigated.

• Section on Organelle Biochemistry—Dr. Martin Flavin

This section studies the structure, assembly, and function of selected eukaryotic cell organelles and the physiological regulation of assembly and function. At this time the major emphasis is on the mechanism of polymerization of microtubules in brain and unicellular organisms.

Laboratory of Cellular Metabolism—Dr. Martha Vaughan

• Section on Metabolic Regulation—Dr. Martha Vaughan

Research concerns mechanisms of hormone action with emphasis on the enzymes involved in synthesis and degradation of cyclic nucleotides.

• Section on Cellular Pharmacology—Dr. Michael A. Beaven

Research centers on the release of histamine, serotonin, and other factors during inflammatory and allergic reactions, the enzymes participating in the

synthesis and degradation of these substances, and the effect of anti-inflammatory agents on cell proliferation and chemotaxis.

• Section on Biochemical Physiology —Dr. Vincent C. Manganiello

Research is concerned with the action of certain peptide hormones, glucocorticoids, and prostaglandins on growth and function of mammalian cells, especially cultured cells.

• Section on Molecular Mechanisms —Dr. Joel Moss

Research is concerned with the molecular basis for regulation of enzymes involved in cyclic nucleotide metabolism, e.g., subunit structure, covalent modification, effector interactions.

Laboratory of Chemical Pharmacology—Dr. James R. Gillette

• Section on Drug-Enzyme Interaction—Dr. James R. Gillette

The interests of this section center on various aspects of drug disposition including the relationship between drug metabolism and drug toxicity. Its main objectives have been understanding the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites.

• Section on Physiology—Dr. Harriet M. Maling

This section studies interactions of drugs, particularly the mechanisms by which various treatments may alter the hepatotoxicity or pulmonary toxicity induced by various organic compounds. It includes studies on the relationship between hepatotoxicity and covalent binding of metabolites to liver lipids and proteins, the formation of lipid peroxides, and effects on microsomal enzymes. It also includes studies of toxicity modifications produced by treatments which alter substantially the body clearance of a compound.

• Section on Drug-Tissue Interaction—Dr. Gopal Krishna

This group is involved in the study of the initial events occurring in cells as the result of a variety of drug-hormone cell interactions, including the role of cyclic nucleotides as mediators of a variety of hormone actions. Recently, this section has become involved in the investigation of the biochemical mechanisms that may be involved in drug-induced tissue lesions.

Laboratory of Chemistry—Dr. Henry M. Fales

This laboratory conducts research into methods for the structural analysis of organic compounds, specifically via mass spectrometry, X-ray crystallography, nuclear magnetic resonance, in addition to classical methods of chemical degradation. Also biosynthetic pathways are studied using tracer techniques and chemical synthesis.

• Section on Physiological Chemistry—Dr. John I. Pisano

Normal and pathologic states in man are studied at the molecular level by advanced analytical techniques. Under investigation are neuroactive enkephalins and the prostaglandins and vasoactive peptides (bradykinin and angiotensin), precursor proteins of the peptides kininogens and the enzymes kallikreins involved in their biosynthesis and degradation. Research is currently directed to the study of hypertension, coagulation, and fibrinolysis, micromethods for the detection and amino acid sequence analysis of polypeptides, and the discovery of naturally occurring active peptides.

• Section on Chemical Structure —Dr. Henry Fales

This group isolates and identifies biochemically important and structurally interesting organic compounds using gas, liquid, high pressure, and thin layer chromatography in conjunction with mass spectrometry, nuclear magnetic resonance and X-ray crystallography. The section

also develops and extends methodology in above fields.

- Section on Structural Nuclear Magnetic Resonance—Dr. Robert H. Highet

The section emphasizes the development and use of new techniques to study the structure and chemical characteristics of compounds of biological interest. The structure of metabolites of steroidal drugs and alkaloidal toxins and the factors influencing aromatic-alicyclic tautomerism are typical areas for investigation.

Laboratory of Experimental Atherosclerosis—Dr. Donald L. Fry

The laboratory program is directed toward experimental evaluation of the pathological, physiological, biophysical, chemical, and histological processes involved in the genesis of atherosclerosis. These studies are carried out with tissues from animal colonies and human subjects.

- Section on Vascular Physiology —Dr. Donald L. Fry

Studies on the relationship of physical-chemical and hemodynamic forces in the genesis and regression of atherosclerosis are the focus of this section. These include studies on vascular injury, arterial cellular responses to various mechanical and chemical events, vascular rheology, and the processes of mass transport into and out of arterial tissue.

Laboratory of Kidney and Electrolyte Metabolism—Dr. Maurice B. Burg

- Section on Electrolyte Transport—Dr. Jack Orloff
- Section on Renal Mechanisms—Dr. Maurice B. Burg
- Section on Membrane Metabolism—Dr. Joseph S. Handler

This laboratory conducts research on the mechanism and regulation, hormonal and otherwise, of a variety of transport processes in systems including the intact kidney, isolated perfused segments of renal tubules, toad bladder, and erythrocytes. Electrophysiology and intermediary metabolism as related to transport are emphasized.

Laboratory of Molecular Hematology—Dr. W. French Anderson

This laboratory is concerned with investigation into the mechanism and regulation of mammalian gene expression and protein synthesis. Areas of research include molecular cloning of globin genes, cell-free transcription of cloned globin genes, gene transfer of globin (and other) genes by physical microinjection and cellular transformation techniques, studies on globin gene expression using mouse erythroleukemia cells and somatic cell hybrids. Joint studies are also carried out with the Clinical Hematology Branch.

Laboratory of Technical Development—Dr. Robert L. Bowman

This laboratory conducts research on instrumentation and methodology applicable in heart and biomedical research. The scope of the program extends from highly specialized research ultramicromethods to practical clinical instrumentation.

- Section on Biophysical Instrumentation—Dr. Robert L. Berger

This section develops methods and instruments based on new physical and computer science technology to measure reaction kinetics, molecular structure and chemistry of substances of biomedical interest. Current work involves developing calorimetric, Mossbauer spectroscopic, laser photolysis, fast spectroscopic and fluorometric systems.

- Section on Pulmonary and Cardiac Assist Devices—Dr. Theodor Kolobow

This section conducts a program to develop and clinically apply devices for extracorporeal support of the respiratory and circulatory systems. This includes the development of improved blood oxygenators, blood pumps, and control systems.

National Institute of Allergy and Infectious Diseases

Richard M. Krause, M.D.,
Director
Kenneth W. Sell, M.D., Ph.D.,
Scientific Director
Michael M. Frank, M.D.,
Clinical Director

Clinical and Research Associates

The National Institute of Allergy and Infectious Diseases (NIAID) annually appoints associates for the laboratories described below. Clinical associates are selected by the clinical director, appointed to the Laboratory of Clinical Investigation, and begin after at least 1 year of residency training. Research associate appointments in the other laboratories may begin after internship or residency training. In general, appointments to the Laboratory of Clinical Investigation carry responsibility for patients in the research program but are not otherwise different from those which begin after internship.

Specific answers to any questions or additional information may be obtained by applicants from the Scientific Director, NIAID, National Institutes of Health, Bethesda, MD 20205. This can include rosters of scientific staff, summaries of research, or information about possible opportunities not listed under the laboratories. In writing, please be as specific as possible as to interests and information desired.

Clinical Branch

Laboratory of Clinical Investigation—Dr. Michael M. Frank

The NIAID appoints six to eight clinical associates. Appointments are made for 3 years. Ward medical care duties occur during the first year, and no assigned primary clinical responsibilities are made during the second or third year except as directed by the needs of the clinical associates' research.

There are 52 research beds. Clinical associates consult on clinical infectious disease problems in other Institutes and at the National Naval Medical Center. Each clinical associate selects an area of investigative interest under the general preceptorship of the clinical director and the senior members of the staff of the Laboratory of Clinical Investigation. Emphasis is placed on the conduct of laboratory and clinical research designed to provide the basic training necessary for a career in clinical investigation. Depending upon the area in which the clinical associate works, the subspecialty boards in infectious diseases or allergy will usually credit the training received towards admission to these board examinations. Final identification of positions for which they are being considered and whether the position will require 1 or more years of residency training before entry will be explained to prospective candidates at the time of interview.

Opportunities exist for research in a wide variety of areas of infectious, allergic, and immunological disease. Examples of studies now in progress are:

- The etiology and pathogenesis of certain viral infections in man.
- The role of certain host defense mechanisms in prevention of infections.
- Pathogenesis and treatment of granulomatous diseases and vasculitis.

- Etiology and pathogenesis of the idiopathic hypereosinophilic syndrome.
- Cellular immunity and delayed hypersensitivity in systemic mycoses.
- The role of the granulocyte in resistance and response to infection.
- Mechanisms of immune damage and the role of complement in immunological reactions.
- Mechanisms of regulation of immune reactivity in normals and in patients with immunologically mediated diseases.
- The biochemical response in lymphoid cells following antigenic stimulation in normal and immunologically impaired subjects.
- The biochemical, neurophysiologic, and immunologic abnormalities of asthma and allergic diseases.
- The role of immune complexes in the production of disease.
- Immunopathologic mechanisms in parasitic infections.
- The pathogenesis of cold urticaria, cholinergic urticaria, and chronic idiopathic urticaria and angioedema.
- The effect of corticosteroids and cytotoxic agents on lymphocyte subpopulations.
- Laboratory and clinical evaluation of antiviral substances.

Further information can be obtained if inquiries with specific questions are addressed to Dr. Kenneth W. Sell, Scientific Director.

Research Areas and Senior Staff:
Allergic Diseases—Michael A. Kaliner, M.D.
Bacterial Diseases—John I. Gallin, M.D.
Clinical Allergy and Hypersensitivity—Charles H. Kirkpatrick, M.D.
Clinical Immunology—Michael M. Frank, M.D.
Clinical Mycology—John E. Bennett, M.D., Kyung J. Kwon-Chung, Ph.D.
Clinical Parasitology—Franklin A. Neva, M.D., Eric A. Ottesen, M.D.
Clinical Physiology—Anthony S. Fauci, M.D.
Medical Virology—Stephen Straus, M.D.

Basic Research Laboratories

Laboratory of Viral Diseases—Dr. Wallace P. Rowe

This group of scientists conducts research on the basic biology and ecology of chronic and persistent virus infections, with particular emphasis on oncogenic viruses, and on host antiviral defense mechanisms.

Studies of tumor viruses are concentrated on murine leukemia viruses, adenovirus-simian virus (SV) 40 hybrid viruses, and human papovaviruses. These studies include investigations of the interactions between defective and competent viruses, the natural history and epidemiology of tumor viruses, genetic transmission of leukemia viruses in mice, and the viral and host genetic factors of importance in viral tumorigenesis.

The mechanism of action of interferon and inducers of interferon is studied by biological and biochemical approaches; the development and evaluation of new interferon inducers for possible clinical application are also undertaken.

Other areas of study are the biology of parvoviruses and the recently discovered viruses of certain medically important protozoa.

Research Areas and Senior Staff
Leukemia Viruses—Wallace P. Rowe, M.D., Janet W. Hartley, Ph.D.
Adeno-SV40 Hybrid Viruses—Andrew M. Lewis, Jr., M.D.
Papovaviruses—Kenneth K. Takemoto, Ph.D.

Parvoviruses—Malcom D. Hoggan, Sc.D.
Interferon—Hilton B. Levy, Ph.D.
Amebal Viruses—Carl F. T. Mattern, M.D., M. Katherine Cook Jaouni, Ph.D.

Laboratory of Biology of Viruses—Dr. Norman P. Salzman

The investigations in this laboratory are primarily concerned with the molecular events involved in virus replication. Investigations are also conducted to define the basis for the pathogenic effects of viruses on cellular functions. Biosynthesis of the nucleic acid, protein, and carbohydrate components of virus particles and factors governing their assembly are under study as is the mode of action of certain antiviral substances. These studies are carried out with both lytic and oncogenic viruses. The mechanisms by which normal cells are transformed to an oncogenic state is an important area of investigation. Fundamental biochemical and biophysical studies are also carried out with uninfected cells.

Parallel studies to those on viral synthesis seek to define the physical and chemical makeup of the purified virus itself, utilizing electron microscopy, ultracentrifugation, and nucleic acid and protein analysis.

Other programs investigate the isolation and characterization of mutated viruses. Studies are conducted on the relationship between mutation in the viral genome and biochemical alterations in the infectious cycle.

The staff includes persons trained in biochemistry, medicine, microbiology, physical chemistry, and organic chemistry. The program for associates is designed to provide them with a full understanding of modern trends in molecular biology and to enable them to apply biochemical and biophysical methods in dealing with fundamental problems in virology, cell biology, and medicine.

Research Areas and Senior Staff
Biochemical Virology—Norman P. Salzman, Ph.D.
Macromolecular Biology—Bernard Moss, M.D., Ph.D., Frank Defilippes, Ph.D.
Molecular Structure—James A. Rose, M.D., Claude F. Garon, Ph.D., Lois A. Salzman, Ph.D., Edwin D. Sebring, Ph.D.

Laboratory of Infectious Diseases—Dr. Robert M. Chanock

This laboratory's activities are concerned with the basic behavior of viral and mycoplasmal pathogens which play an important role in acute infectious diseases of man. The importance, disease manifestations, and ecologic properties of various respiratory tract and gastrointestinal tract pathogens are defined during the study of individuals with naturally acquired disease. Supplementary information is obtained from detailed investigation of experimentally infected volunteers in an attempt to define the pathogenesis of disease and the factors involved in the hosts' resistance to both infection and illness. The techniques of microbial genetics are employed to study the nature of virulence and to select attenuated mutants which are then evaluated for their usefulness in vaccination against natural disease.

Biophysical techniques are used to define the subparticulate structure of viruses and to search for certain fastidious agents, such as coronaviruses, acute gastroenteritis viruses, and hepatitis viruses, which cannot be detected in standard tissue culture systems. Appointees can expect to receive training in basic biophysical and biological characterization of viruses and mycoplasmas, microbial genetics, immunologic methods used in the study of respiratory tract disease and epidemiologic techniques employed in defining the ecology of agents which cause acute infectious diseases. Some appointments are for 3 years.

Research Areas and Senior Staff
Epidemiology—Albert Z. Kapikian, M.D.
Hepatitis Virus—Robert H. Purcell, M.D.
Mycoplasma—Joseph G. Tully, Ph.D.
Respiratory Viruses—Robert M. Chanock, M.D.

Laboratory of Immunogenetics
—Dr. Thomas J. Kindt

This group is involved in basic research on major gene complexes involved in immune function. These are immunoglobulin genes that give rise to antibody diversity and genes at the major histocompatibility locus that encode cell surface antigens involved in graft rejection and numerous other immune functions.

The approaches used in these studies emphasize structural, serological, and genetic investigations and the techniques used include quantitative radioimmunoassays, protein and carbohydrate structure determinations by conventional and microchemical methods, and a variety of immunologic assays for cellular and humoral components of the immune response.

Areas of active investigation include: studies on the inheritance of immunoglobulin genes employing highly specific idiotypic and allotypic antisera directed against markers present on homogeneous antibodies; structural studies on immunoglobulins and homogeneous antibodies isolated from the rabbit; radiochemical amino acid sequence analysis of histocompatibility antigens from mouse tumor cells; genetic and structural investigations on components from lymphoid cell membranes; and molecular biological studies of messenger RNA encoding H and L chains.

In addition, the Immunobiology Section of the laboratory will study the role of the major histocompatibility complex in the control of responses to individual antigens or infectious agents and will evaluate relationships between histocompatibility types of humans and pathogenicity or virulence of infectious disease processes.

The opportunity is available for associates to study in any of these areas under the preceptorship of a senior laboratory member. During their tenure, appointees become proficient in modern techniques of structural biochemistry, and in quantitative and qualitative immunologic procedures. In addition, they gain an understanding of the genetic mechanisms underlying the ability to mount an immune response.

Research Areas and Senior Staff
Immunoglobulin Genetics—T. J. Kindt, Ph.D., J. A. Sogn, Ph.D.
Membrane Antigens—J. E. Coligan, Ph.D.
Structural Biochemistry—
H. Krutzsch, Ph.D.
Immunobiology—K. W. Sell, M.D., Ph.D.

Laboratory of Immunology—
Dr. William E. Paul

This laboratory is engaged in the study of various aspects of cellular immunology, immunogenetics, and immunochemistry, particularly as they bear on a fuller understanding of the biological significance of the immune response and on the role of immune mechanisms in the prevention and pathogenesis of human disease.

Areas of active investigation include the origin, development, functional diversity, and mechanisms of activation of lymphocytes; the genetic control of specific immune responses and of interactions between immunocompetent cells; the nature and specificity of antigen-binding receptors of lymphocytes; the chemistry of allotypic and idiotypic determinants of rabbit and mouse immunoglobulins and the use of such determinants to study the genetic control of immunoglobulin synthesis; and the degree of specialization of individual immunocompetent cells.

Further, studies of the role of different lymphocyte classes in many

human diseases are underway, and models for the study of cellular immune responses in tumor immunity and for the investigation of immunotherapy of tumors are being developed.

Associates will have the opportunity to participate in studies in one or more of these areas under the preceptorship of one of the senior members of the laboratory. In the course of their work, appointees should receive a thorough grounding both in conceptual and technical aspects of immunology.

Research Areas and Senior Staff
Cellular Immunology and Genetic Regulation of the Immune Response —Ira Green, M.D., William E. Paul, M.D., Ronald H. Schwartz, M.D., Ph.D., Ethan H. Shevach, M.D.
Immunochemistry and Immunogenetics—John K. Inman, Ph.D., Rose Lieberman, Rose G. Mage, Ph.D., Myron J. Waxdal, Ph.D.

Laboratory of Microbial Immunity —Dr. Richard Asofsky

The laboratory is primarily concerned with the elucidation of basic mechanisms involved in both the cellular and humoral immune responses to microbial and tissue antigens.

Several major areas of investigation, each employing a wide variety of immunological methods, offer the associate comprehensive exposure both to the theoretical and to the technical aspects of immunology. Mechanisms of induction, control, and ontogeny of immunoglobulin synthesis are being examined in detail. The significance of interaction among different kinds of lymphoid cells in the induction and manifestation of immunity is being studied in graft-versus-host reactions and in humoral immune responses. The development, distribution, and susceptibility of the interacting components to various treatments which suppress or amplify immune reactions are being examined. Methods have been developed for the physical fractionation of lymphoid cells to obtain functionally purified subpopulations.

Autoimmune phenomena are studied using immune complex nephritis as a model. Factors regulating the development and severity of disease and specific methods of preventing or ameliorating disease are investigated. The relationship of this disease to the presence and activity of such integrated viruses as the murine leukemia agents are studied. The nature of the immune response to protozoal parasites, including the antigenic and genetic requirements for the expression of this immunity are studied. In most of the program areas outlined, work *in vivo* is complemented by the use of *in vitro* models.

Research Areas and Senior Staff
Biochemistry—Benjamin Prescott, Ph.D.
Experimental Pathology—Richard Asofsky, M.D.
Microbiology and Immunology —Philip J. Baker, Ph.D.

The Laboratory of Parasitic Diseases—Dr. Franklin A. Neva

This group of scientists is engaged in both basic and applied studies of parasitic diseases, with emphasis upon those affecting man. A variety of protozoan (malaria, trypanosomes, leishmania, amebae and toxoplasma) and helminth (schistosomes, filaria, and strongyloides) parasites are used for experimental work. Current studies include comparative mechanisms of energy transfer, ultrastructure of parasites, host-parasite interactions at both *in vitro* and *in vivo* levels, and *in vitro* culture of certain agents.

Increasing emphasis is being devoted to consideration of immunologic response of the host in parasitic infections, both humoral and cellular. Another area of emphasis concerns the biochemical and immunologic characteristics of parasite surfaces and their interactions with the host cell membrane. Some experimental infections such as leishmaniasis, amebiasis, schistosomiasis and filiari-

sis in animals are used as models of naturally occurring disease in man. The availability of different species of human as well as simian malaria parasites, an insectary and facilities for work with primates provides a unique opportunity to study all stages of the life cycle of the malaria parasite. When appropriate, certain problems that can only be investigated in the field are studied in collaboration with local institutions. Clinical investigators from the Laboratory of Parasitic Diseases are associated with the Laboratory of Clinical Investigation within the Section of Clinical Parasitology. Thus, selected patients can be seen and studied as inpatients or outpatients at the Clinical Center.

Within limits of space and available guidance by a member of the senior staff, associates can select their area of work and a preceptor. In addition, an organized program provides associates with an exposure to clinical parasitology.

Research Areas and Senior Staff
Host-Parasite Relations—Dr. A. W. Cheever
Cell Biology and Immunology—Dr. F. A. Neva, Acting Head
Clinical Parasitology—Dr. F. A. Neva
Malaria Section—Dr. L. H. Miller
Parasite Growth and Differentiation—Dr. L. S. Diamond
Physiology and Biochemistry—Dr. E. C. Weinbach

Laboratory of Streptococcal Diseases—Dr. Roger M. Cole

This laboratory conducts basic studies of bacteria, which currently include streptococci, staphylococci, and mycoplasmas, and some of their viruses. Emphasis is on microbial genetics, phage virology, ultrastructure, chemical and antigenic composition, and production of some toxins. General approaches to study utilize DNA-mediated transformation and transfection, phage-mediated transduction, lysogenization, appropriate bacteriologic and biochemical methods and newer techniques in the molecular biology of bacterial viruses. Present projects involve study of DNA binding and uptake by competent group H streptococci; the role of lysogeny in production of streptococcal pyrogenic exotoxin (erythrogenic toxin); the intracellular site and function of lipoteichoic acid in staphylococci; and the nature of viruses (and their DNA) that occur in acholeplasmas and spiroplasmas.

Associates have opportunities for training and experience in any of the above areas.

Research Areas and Senior Staff
Streptococci and Bacteriophages—Roger M. Cole, Ph.D., M.D.
Microbial Genetics—Jon M. Ranhand, Ph.D.
Microbial Composition and Function—Eskin Huff, Ph.D.; Theodore S. Theodore, Ph.D.
Microbial Ultrastructure—Roger M. Cole, Ph.D., M.D.

Rocky Mountain Laboratories—The Rocky Mountain Laboratories, located at Hamilton, Montana, consist of the following:

Laboratory of Persistent Viral Diseases—Dr. Bruce W. Chesebro

This group is concerned with studies of virus-host interaction with the primary aim of elucidating mechanisms involved in establishment, maintenance and elimination of persistent viral infections. Investigations are also made on involvement of persistent virus infection and autoimmune and immune complex diseases. Appropriate models being examined include rabies virus, scrapie, murine leukemia viruses, and Aleutian disease virus of mink.

Laboratory of Microbial Structure and Function—Dr. John Swanson

Bacteria and rickettsiae pathogenic for man are the major topics for study in this laboratory. Of special interest are those components and products of microorganisms that influence their virulence or pathogenicity. Topics of current study in the laboratory are the following:

- gonococcal surface components

and their genetic control
- surface components of mycoplasma and their modification by viruses
- metabolic and surface characteristics of rickettsiae that influence their intracellular growth and their serological reactivity
- surface components and products of pertussis-causing bacteria
- adjuvant and endotoxic moieties of bacterial cell walls.

Research Areas and Senior Staff
Gonococci—John Swanson, M.D.
Pertussis—John Munoz, Ph.D., R. K. Bergman, Ph.D.
Endotoxic and adjuvant properties of cell walls—Edgar Ribi, Ph.D., Charles McLaughlin, D.V.M., Ph.D.
Rickettsiae—Robert Anacker, Ph.D., Jimmy Williams, Ph.D.

Epidemiology Branch—Dr. Robert Philip

The staff of this branch plans and conducts epidemiologic investigations and studies on natural histories of human diseases. The senior staff provides consultative services on biometric analysis and epidemiologic methods to other investigators and provides seroepidemiologic and diagnostic support for the branch and selected collaborative projects outside of the branch. One research group performs surveillance of arthropod-borne agents of human disease importance. Another group undertakes detailed histopathologic investigations of naturally occurring diseases in animals, naturally occurring slow viral diseases of animals, and infectious problems in animal models which may be related to findings in counterpart diseases of man.

Research Areas and Senior Staff
Epidemiology—Dr. Robert Philip, Dr. Leo A. Thomas, and Elisabeth A. Casper.
Arthropod-borne Diseases—Dr. Willy Burgdorfer, Dr. Carleton M. Clifford, Dr. Conrad Yunker, and Dr. James Keirans
Histopathology—Dr. William Hadlow

National Institute of Arthritis, Metabolism, and Digestive Diseases

G. Donald Whedon, M.D.,
Director
J. E. Rall, M.D., Ph.D.
Director of Intramural Research
Philip Gorden, M.D.
Clinical Director

Clinical Associates

Each clinical associate is assigned to one of the Institute's clinical branches or sections, within which he carries out both clinical work and laboratory studies. The associate is, in effect, an apprentice investigator, working both on the wards and in the laboratory under the guidance of an experienced preceptor. The associate is encouraged to choose his or her own problem for independent investigation, if facilities required for its successful pursuit and if technical advice and supervision necessary are available. In addition, the associate provides professional care for research patients admitted to the service of the branch chief and assists in the outpatient department. There is considerable variation among the branches of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) with respect to the proportion of the associate's time required for patient care activities.

Clinical associates of the Clinical Endocrinology, Diabetes, and Metabolic Branches participate in a 3-year Interinstitute Endocrinology Training Program which will satisfy requirements for Endocrinology Subspe-

cialty Board Examinations. In certain instances, when positions are available, other NIAMDD clinical associates may spend a third year in the Endocrinology Program.

The Institute recruits about 10 new clinical associates each year. The assignments are for 2 or 3 years and usually are not extended. One year of internship and at least one year of residency should generally be completed before the appointment begins.

Vacancies do not necessarily occur within each program each year; the Program Area Selection Checklist indicates the positions to be filled. The chiefs of branches or sections with openings and the clinical director screen applications and select candidates for personal interviews. After the results of matching are announced, each successful candidate is asked to confirm acceptance of the position.

The clinical research branches are listed below with the names of the permanent investigators and a brief sketch of the areas of interest. Prospective applicants desiring more information should write to Dr. Philip Gorden, Clinical Director, NIAMDD, Building 10, Room 9N222, NIH, Bethesda, Maryland 20205. Supplementary information sheets on each branch, together with selected bibliographic citations are available on request.

Research Associates

NIAMDD has four positions available each year for research associates. These 2-year appointments, usually beginning on July 1, are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. During their stay here, research associates will devote the larger part of their time to laboratory research under the immediate supervision of a preceptor. The chosen candidates are free to choose a preceptor (upon mutual agreement) in any area in the Institute, either clinical or basic research. Should candidates elect a clinical area, they would not participate in clinical care of patients. The research associate, approximately 1 year prior to beginning, will visit NIAMDD to select the laboratory and preceptor with whom he or she wishes to work. Candidates desiring further information about the laboratories, staffs, and bibliography can obtain this by writing Dr. J. E. Rall, Director of Intramural Research, NIAMDD, National Institutes of Health, Bethesda, MD 20205.

Staff Associate in Epidemiology and Clinical Investigations

One or two candidates are chosen each year for a 2 year assignment for studying the epidemiology of chronic disease such as diabetes, arthritis, and cholelithiasis, among the Pima Indians of Arizona. In addition, clinical research opportunities are available in the Clinical Research Center of the Phoenix Indian Hospital. Candidates occasionally begin this associateship upon completion of an internship but, in most cases, more postdoctoral training has been completed. Candidates interested in this possibility are encouraged to write Dr. Peter H. Bennett, Epidemiology and Field Studies Branch, NIAMDD, 1440 E. Indian School Road, Phoenix, AZ 85014, for more detailed information.

Clinical Research Branches

Arthritis and Rheumatism Branch—Dr. John L. Decker

- Section on Connective Tissue Disease—Drs. John L. Decker, John H. Klippel, Paul H. Poltz, Alfred D. Steinberg, and James E. Balow

The pathogenesis of systemic lupus erythematosus (human and mouse models) is under study. Suppressor and activator lymphocyte isolation, development of stable immune complexes, and studies of reticuloendothelial function are in progress. Clinical work is on cytotoxic drugs in lupus nephritis, on survivorship variations with disease pattern, and on effects of drugs upon patients with lupus or rheumatoid arthritis. Cytopheretic and plasmapheretic techniques are being studied in patients with connective tissue disease.

- Section on Chemical Immunology—Dr. Henry Metzger

The section is involved in fundamental research on the structure and mechanism of immunoglobulins and their receptors on cells, using protein chemistry, immunochemistry, tissue culture and electronmicroscopy techniques.

Clinical Endocrinology Branch—Drs. Jacob Robbins, Jan Wolff, Saul Rosen, Harold Edelhoch, and Bruce Weintraub

Activities in this branch range from basic laboratory research to clinical investigations. A broad spectrum of endocrinology is covered, with emphasis on thyroid and polypeptide hormones. Laboratory research includes fundamental and applied protein chemistry including studies on hormone transport proteins and polypeptide hormones, the mechanism of hormone actions, control mechanisms in secretory cells, adenylate cyclase-receptor interactions and membrane biochemistry, and the biosynthesis of polypeptide hormones.

Clinical Hematology Branch—Dr. N. Raphael Shulman

Laboratory work concerns the biochemistry of blood coagulation, platelet physiology and metabolism, and various problems in the field of immunohematology. Interests currently include isolation and characterization of antihemophilic factors, correlation of platelet metabolism with function involving analyses of membrane reactions and secretory phenomena, and studies of immunologic mechanisms of platelet injury, including drug- and allo-immune problems. Clinical work involves patients with hemorrhagic and immunologic disorders relevant to the laboratory studies.

- Section on Cell Biology and Biochemistry—Dr. Harvey B. Pollard

The primary interest of this group is in mechanisms of secretion of proteins, hormones, and transmitters from neuroendocrine and other cells. Problems under investigation currently include how calcium acts to fuse secretory vesicles to plasma membranes, and how release of vesicle contents during exocytosis subsequently occurs. Special interest is placed on proteins such as synexin that may mediate such events, on the relation of cytoskeletal elements to secretory functions and on ion transport sites in vesicle and plasma membranes that may be important in regulating secretion.

Diabetes Branch—Drs. Jesse Roth, Phillip Gorden, and C. Ronald Kahn

Focus is on peptide hormones, especially insulin, growth hormone and insulin-like growth factors. Recent work has been largely on the interaction of the peptide hormones with their receptors on the surface membrane of target cells. The emphasis is on diseases where the concentration or affinity of the receptor changes in response to intracellular or extracellular events. A broad range of experimental approaches is used to explore these processes including cell culture, purification of hormones and of membrane components, and studies

of rodents and people with a wide variety of insulin-resistant conditions.

Digestive Diseases Branch—

- Section on Gastroenterology—Drs. Jerry D. Gardner, Denis M. McCarthy, and Robert T. Jensen

Laboratory and clinical programs focus on gastrointestinal endocrinology and on the regulation of secretory, absorptive, propulsive and immunological processes throughout the GI tract. Studies employ *in vivo* techniques, both in patients and in animals, and a wide variety of *in vitro* techniques from the disciplines of cell biology, biochemistry, and immunology.

- Section on Diseases of the Liver—Drs. E. Anthony Jones and Jay H. Hoofnagle

Both laboratory and clinical investigations are focused upon the etiology, immunology and treatment of chronic hepatitis and primary biliary cirrhosis. Laboratory research includes studies of cellular immunology and the modulation of immune responses in primary biliary cirrhosis and other chronic liver diseases; investigation of the role of various viral antigens and antibodies in chronic HBsAg-positive hepatitis; study of the metabolic behavior of alpha-1-antitrypsins of different molecular structure; characterization of cell surface receptors on isolated hepatocytes and Kupffer cells; and analysis of therapeutic manipulations for the treatment of fulminant hepatic failure in an animal model. Clinical investigations include studies of the natural history of chronic HBsAg-positive hepatitis and chronic non-A, non-B hepatitis. The treatment of primary biliary cirrhosis with immunosuppressive agents and HBsAg-positive chronic hepatitis with antiviral agents is undergoing preliminary investigation.

Genetics and Biochemistry Branch—Drs. Elizabeth F. Neufeld, R. Daniel Camerini-Otero, and Michael A. Zasloff

The branch conducts studies in biochemical and molecular genetics which range from the very basic (eukaryotic gene isolation and organization, the control of gene expression, gene transfer, and the biochemical basis of lysosomal storage disorders) to the highly applied (development of new diagnostic tests and carrier detection for a number of genetic diseases). The branch also conducts clinical genetics activities and participates in the NIH Interinstitute Genetics Program.

Metabolic Diseases Branch—Drs. Gerald D. Aurbach, Stephen E. Marx, and Allen M. Spiegel

Laboratory investigations are directed to hormone-receptor interactions, regulation and characterization of adenylate cyclase, and cellular responses to hormones, particularly catecholamines, parathyroid hormone and calcitonin. The clinical program involves studies of patients with disorders of mineral metabolism. Patients with hyperparathyroidism are evaluated with arteriography, selective thyroid venous catheterization, and radioimmunoassays for parathyroid hormone and cyclic AMP in plasma and/or urine. Excised parathyroid tissue is available for *in vitro* studies on control of hormone secretion and for cryopreservation and use in management of postoperative hypoparathyroidism with parathyroid autotransplantation.

Pediatric Metabolism Branch—Paul A. di Sant'Agnese

Cystic fibrosis of the pancreas is the target of both laboratory and clinical work. Glycoproteins, polyamines, the circulating "cystic fibrosis" factors and other substances are analyzed for their possible relationship to the pulmonary, pancreatic, and sweat gland involvement as well as other facets of this genetic disease. Techniques used include tissue culture, amino acid analyses, automated ion exchange and thin-layer chromatography, radioisotope analyses by liquid scintillation counting and tissue culture. A variety of clinical as-

pects such as vitamin E deficiency, the renin-aldosterone axis, and cyclic nucleotides are studied and the course and complications of cystic fibrosis are documented.

Phoenix Clinical Research Unit—Dr. Peter H. Bennett

Diseases unique to or particularly prevalent among American Indians are studied. Current investigations focus on diabetes, gall-bladder disease and lipid disorders and include studies of insulin receptors, hormonal abnormalities in diabetic and prediabetic subjects, lipid and lipoprotein metabolism, and studies of biliary lipid metabolism and physiology in southwestern American Indians. Investigations are carried out at the Phoenix Clinical Research Center, a 24-bed clinical research unit with full supporting laboratory facilities located within the Indian Health Service Referral Hospital in Phoenix, Arizona.

Basic Research Laboratories

Laboratory of Biochemical Pharmacology—Drs. Herbert Tabor, Simon Black, Victor Ginsberg, Leonard D. Kohn, and Kolomon Laki

The work of this laboratory includes a large variety of biochemical and physiological investigations. Included are studies on polyamine synthesis and action, nucleic acid and protein biosynthesis, tryptophan biosynthesis, the structure of cellular membranes, and yeast and *Escherichia coli* genetics. One section is concerned in particular with the structure, function, and bioenergetics of biological membranes and the mechanism by which various effectors—hormones, toxins, neurotransmitters, interferon, and viruses—transmit their information through these membranes to the interior of the cell. Another subsection studies diverse aspects of the related hormones insulin and somatomedin, including: structure, biosynthesis, mechanism of action, biological role, and genetic syndromes of hormone resistance. A third section is particularly concerned with the biology of the complex carbohydrates of animal cell surfaces.

Laboratory of Biochemistry and Metabolism—Drs. G. Gilbert Ashwell, William B. Jakoby, and Yale J. Topper

The laboratory program is directed toward an understanding of the basic biochemical mechanisms involved in both normal and abnormal biological processes. Within this general framework, independent projects cover a broad range of biochemical investigations.

A brief summary of the major areas under study includes an examination of the hormone-dependent differentiation and development of mammary gland tissue in normal and hypophysectomized rats; a detailed study of growth and development whereby the formation of the primary septum of yeast is used as a molecular model for morphogenesis; the isolation and characterization of specific hepatic receptors which regulate the metabolism of serum glycoproteins; and a study of the cluster of enzymatic activities classified as the glutathione S-transferases which function as one of the major detoxification systems in mammals and the role of cellular factors involved in the biosynthesis and differentiation of lymphocytes in spleen and thymus. In addition to the above general areas, specific projects of individual investigators include a study of the particulate enzymes involved in carbohydrate metabolism, identification of sulfur-containing nucleotides in tRNA, biochemical abnormalities in human cystinosis, genetic control of bacterial membrane proteins, and thermodynamic and kinetic studies on enzymatic mechanisms.

Laboratory of Bioorganic Chemistry—Drs. John W. Daly and Donald M. Jerina

This laboratory's research mission is to elucidate the mechanism of interaction of pharmacologically active substances with biological systems. Research is designed toward the development of new chemical agents as tools for the study of membrane and cytosol functions of cells. New mechanisms of action or metabolism of such agents are also investigated for their potential use as therapeutics. Development and application of modern techniques of organic chemistry for the synthesis, separation, and spectral investigation of these chemical agents and their interactions with macromolecules are emphasized. The goal is to provide insights into the normal and pathological function of biological systems and to delineate the metabolic formation, fate, and action of physiologically active agents, such as amino acids, biogenic amines, cyclic nucleotides, hormones, neurotransmitters, and steroids. Studies include pharmacologically active agents such as natural products, therapeutic agents, toxins, carcinogens, and mutagens.

Laboratory of Chemical Biology—Drs. C. B. Anfinsen, Alan N. Schechter, Hiroshi Taniuchi, Edward Steers, and Irwin Chaiken

Research in this laboratory is concerned with the three-dimensional structure of proteins and the relationships between structure and function. One set of studies being carried out by Dr. Taniuchi, and to some extent by Dr. Chaiken, involves the interaction between fragments derived from particular proteins that have the capacity to interact noncovalently with the regeneration of native structure and function. A second model system concerns sickle cell hemoglobin and fetal hemoglobin. In this work, by Dr. Schechter and his group, attempts are being made to understand the nature of abnormal physical and physiological properties in terms of structure and to develop means for detecting small amounts of such abnormal molecules in the biological material, and in the case of sickle cell hemoglobin, to test the capacity of various amino acids and small peptides to correct the structural and functional lesion. Another group is currently involved with the isolation and characterization of human interferon and hopes eventually to determine the structure of this substance and synthesize it. Finally, Dr. Steers and his colleagues are investigating membrane properties using the paramecium as the test object.

Laboratory of Chemical Physics—Drs. Edwin D. Becker, Paul D. Altland, Elliot Charney, William A. Hagins, William A. Eaton, and Dr. Ira W. Levin

Research in this laboratory is characterized by the application of sophisticated physical techniques to the solution of a wide range of problems. Among the current research interests of the staff are: analysis of the kinetics and mechanism of aggregation of hemoglobin-S; study of the association of mononucleotides and of the conformational behavior of polynucleotides; investigations of the excitation of visual photoreceptors and resultant ionic processes in membranes; analysis of excited electronic states of small molecules in the vapor phase and in molecular beams; development of methods for asymmetric synthesis; and study of the structural characteristics of model membrane systems. Much of the research involves the use of a variety of spectroscopic methods—for example, nuclear and electron magnetic resonance, laser-Raman and resonance Raman spectroscopy, electric-field-induced dichroism and ultraviolet and visible microspectrophotometry.

Laboratory of Chemistry—Drs. Bernhard Witkop, L. A. Cohen, A. Brossi, C. P. J. Glaudemans, and D. Johnson

In the oldest laboratory of the Institute (founded June 20, 1905),

chemistry is represented in its broadest context in five independent sections investigating the mechanisms of enzymatic reactions and their simulation, medicinal chemistry, immunochemistry, novel toxins, metabolism, antiviral agents, interferon and analysis and instrumentation. Some of the recent achievements concern the role of retinoids in bladder cancer; effects of novel colchicine derivatives on microtubules; separation of addictive from analgesic properties in new synthetic morphine substitutes; characterization of sodium channels in electrogenic membranes by a frog toxin; the acetylcholine receptor; development of fluorinated amino acids and biogenic amines as selective probes and inhibitors of enzymatic and metabolic processes; hypoxic cell sensitizers; cytotoxic agents selective for cancer cells; the interaction between antigens and monoclonal antibodies; recombinant hybrid immunoglobulins and the detailed structure of fungal antigens; chemistry and biochemistry of interferon induction and interferon-related enzymes.

Laboratory of Experimental Pathology—Drs. Robert M. Friedman, George G. Glenner, Ned Feder, J. H. Tjio, and Lois Tice

The laboratory carries out basic studies broadly relating to the pathogenesis of various disease states. Typical of research projects now underway are: molecular biology of the transcription of a viral genome; mechanism of action of interferon; cytogenetics and immunology; pathogenesis of amyloidosis; genetics and neurobiology; and ultrastructural analysis of cellular function. Techniques used include gel electrophoresis, chromatographic procedures, ultracentrifuge analysis and separation, conventional histopathology and electronmicroscopy, tissue culture, viral assays, cytogenetics, and freeze-etching electronmicroscopy.

Laboratory of Molecular Biology—Drs. Martin Gellert, Jun-ichi Tomizawa, Gary Felsenfeld, David R. Davies, Robert Martin, H. Todd Miles, and Terrell Hill.

The work of the laboratory is concerned with understanding biological processes in terms of structure and reaction at the molecular level. Research includes direct investigations of biological processes, such as genetic recombination, DNA replication, and protein synthesis, studies of the mechanism of transformation by SV40 (a virus causing tumors in hamsters), and studies of the mechanism of hemoglobin S gelation, the phenomenon which causes sickling of red blood cells in sickle cell anemia. Other investigations are concerned with the structure and chemical properties of biologically important materials. These include studies of the organization of DNA and proteins in chromatin, investigations of protein structure by X-ray diffraction, and of nucleic acid and polynucleotide structure by diffraction and spectroscopic methods, and theoretical studies of the mechanisms of free energy transduction, muscle contraction, membrane properties, and biochemical kinetics.

Laboratory of Nutrition and Endocrinology—Drs. Martin Rodbell, John G. Bieri, Bernard T. Kaufman, Robert O. Scow, and Robert T. Simpson

This laboratory consists of five sections devoted to various biochemical and physiological investigations. The Section on Nutrition carries out studies on the role of tocopherols in cellular oxidative processes and on the intermediary metabolism of lipids, carbohydrates, and amino acids in the small intestine. The Section on Endocrinology investigates hormonal regulation of enzymes involved in chylomicron uptake and metabolism in adipose and mammary tissue, the influence of hormones on cellular development and metabolism, and the disposition of fat and metabolites in the cell as viewed from ultrastructural studies. The Section on Vitamin Metabolism investigates the

structural and functional aspects of dihydrofolic reductase and other enzymes involved in folic acid metabolism. The Section on Membrane Regulation studies the mechanism of action of hormones on adenylate cyclase and other membrane regulatory processes. The Section on Developmental Biochemistry investigates the structure and function of chromatin and the regulation of gene function by hormones.

Laboratory of Physical Biology
—Drs. R. J. Podolsky and J. Buck

This laboratory carries out a broad range of studies. The mechanism of muscle contraction is studied in intact cells and in simplified preparations, using time-resolved X-ray diffraction in conjunction with mechanochemical techniques. Activation of muscle cells is examined by measuring calcium movement between the myofilaments and the sarcoplasmic reticulum in skinned muscle fibers. Lipid dispersions in water are investigated as models of the structure and physical states of lipids in cell membranes. Other subjects under investigation are enzyme organization in unicellular organisms, metamorphosis in insects, human red cell sickling, and biological rhythms and entrainment.

Mathematical Research Branch
—Dr. John Z. Hearon

The branch conducts research on the mathematical and theoretical aspects of biological problems and the development of analytical and numerical methodology underlying such an approach. The research programs are designed to provide a formal basis and theoretical apparatus for the rational analysis and quantitative interpretation of biological phenomena. *Research is organized around biological subject-matter areas rather than around subdisciplines of mathematics.* Major research topics include transport and consumption of substrates at the tissue-capillary level; electrotonus in dendritic systems; neuroelectric signaling; bifurcation and stability studies with special reference to propagation of nerve impulse and diffusion-reaction systems; kinetics and thermodynamics of metabolic systems; problems in linear algebra arising from linear kinetics of physiological systems; and mathematical modeling of renal functions.

National Institute on Aging

Robert N. Butler, M.D.,
Director
Richard C. Greulich, Ph.D.,
Scientific Director
Reubin Andres, M.D.,
Clinical Director

Clinical, Research and Staff Associates

The Intramural Research Program of the National Institute on Aging (NIA) is located at the Gerontology Research Center in Baltimore, Md.

The multidisciplinary program of the center, located on the campus of Baltimore City Hospitals, offers 2-year clinical, research, or staff associate training. Preference is given to candidates who intend to pursue careers in investigative and academic medicine. With appropriate approval, associates may participate in clinical activities of the Baltimore City Hospitals and the nearby Johns Hopkins Hospital. Two-year associate appointments may be extended in special instances to 3 years. On occasion, such extended programs, which include clinical experience, may serve to qualify the individual for certification by a subspecialty board, such as endocrinology.

In addition to the 2-year appointments, a 3-year program of clinical and research training in collaboration with the Division of Cardiology, Department of Medicine, Johns Hopkins University, or the Department of Medicine, Baltimore City Hospitals, is offered to a limited number of candidates each year. Under this program, the associate spends the first year in clinical training as a resident physician or clinical fellow in one of the above departments. The second and third years are spent in clinical or laboratory research on gerontology at the center.

Associates are encouraged to participate in a seminar conducted by the NIA center's staff who present a comprehensive view of research in aging. Weekly research conferences are presented by staff members and invited lecturers.

A primary resource for clinical investigation on human subjects is the Baltimore Longitudinal Study of Aging. The subjects are volunteers, 20 to 90 years old or more, who reside in the community, who return for extensive studies every 1 to 2 years, spend 2½ days as inpatients each visit, and are enrolled for their entire lives. The study on men is now of 22 years duration and involves 650 active participants; the study on women began in 1978 and its size will eventually be comparable to the male sample. Associates share in the examination of these participants.

In support of its research program, the center maintains extensive animal colonies to provide rats, dogs, and rabbits of known age, including senescent animals. Animal operating rooms are available as well as shops for the design and construction of special equipment and photography and arts services. Computer facilities are also available, and instruction in the use of computers for laboratory research is provided. The library of the center contains one of this country's most extensive collections of literature on aging research as well as standard scientific journals.

Prospective candidates wishing further information should write to either Dr. Richard C. Greulich, Scientific Director, or Dr. Reubin Andres, Clinical Director, c/o the NIA Gerontology Research Center, Baltimore City Hospitals, 4940 Eastern Avenue, Baltimore, MD 21224.

Clinical Research Branches

Clinical Physiology Branch—Dr. Reubin Andres

This branch is primarily concerned with studies on physiologic changes occurring over the entire adult life span. Studies include the quantification of age changes, elucidation of mechanisms underlying these changes, and relationships between aging processes and specific disease states.

- Endocrinology Section—Dr. Robert I. Gregerman

This section conducts studies on the molecular basis of age-related changes of hormone responses, especially those related to the biochemistry of the adenylate cyclase system and hormone receptors; aging and the endocrinology of the reproductive system; and the enzymology and peptide chemistry of the renin-angiotensin system. Clinical studies are conducted on subjects from the Baltimore Longitudinal Study of Human Aging. Studies on rodents are done on a variety of organs; hormone studies are done in animals of all ages.

- Cardiovascular Section—Dr. Edward G. Lakatta

Scientists in this section investigate cardiovascular hemodynamic function in man using noninvasive methods which include studies both in normal and cardiovascular disease states. Studies on isolated cardiac muscle focus on the mechanisms that

govern excitation-contraction coupling. Additional studies investigate the effect of age, hypertrophy, and physical conditioning on electrophysiological, contractile, and biochemical parameters in cardiac muscle. Response to stress such as hypoxia and adrenergic stimulation and other pharmacological interventions are also studied in these animal models.

• Metabolism Section—Dr. Reubin Andres

This section emphasizes research on glucose homeostasis and its endocrine control. Factors controlling insulin secretion, including gastrointestinal insulinotropic hormone, are quantified with the use of the servo-control glucose clamp technique. Clinical investigations in man are concerned with the assessment of interrelations among such variables as chronologic age, obesity, diabetes mellitus and its complications, hemoglobin A1, serum lipids, dietary factors, and physical activity. Biologic rates of aging in multiple systems are also assessed. The isolated perfused rat pancreas preparation supplements human studies.

• Clinical Immunology Section—Dr. William H. Adler

Studies are conducted on the decline in host immune responsiveness that is seen in aging. These studies involve the development of diagnostic procedures for the detection of relative immunodeficiencies in humans and the investigation of the mechanisms of these deficiencies in humans and experimental animals.

• Human Performance Section—Arthur H. Norris

This section supports the Baltimore Longitudinal Study of Human Aging with work in a variety of areas. Body composition studies seek the causes of tissue loss in the aged. Exercise physiology research is designed to determine the causes of reduced physical capacity in old age. Habitual physical activity and nutrition of subjects are monitored. Assessments are made of neuromuscular function, psychomotor capacity, hearing, and vision. Pulmonary physiology is studied in the context of genetic and environmental factors. Other work includes studies of the relationship of blood pressure to psychomotor variables and intelligence; dermatoglyphics in disease, world populations, twins, and aging; and the factors underlying reduced sexual function in the elderly.

Laboratory of Neurosciences—Dr. Stanley I. Rapoport

This laboratory's clinical program investigates regional cerebral metabolism in man in relation to aging and dementia, and correlates cerebral metabolism with changes in cognition and behavior. Positron emission tomography is used with ^{18}F-2-deoxy-D-glucose, a positron-emitting glucose analogue.

Basic Research Laboratories

• Comparative Nutrition Section—Dr. Charles H. Barrows

Scientists investigate the relationship between aging and nutrition in animal populations. The specific areas studied include the effects of age on absorption, distribution, and utilization of known nutrients and the mechanisms responsible for an increased life span associated with dietary restriction. These investigations are done with physiologic, biochemical, and electronmicroscopic techniques. Other studies deal with comparative mammalian biochemistry including investigations of the stability of gene control mechanisms and the characterization of chromatin.

• Experimental Morphology Section—Dr. Richard C. Greulich

This section brings the most modern techniques of microscopy (TEM, SEM) and the related techniques of high resolution autoradiography and

electron and X-ray probe microanalysis to bear on problems of structural-functional relationships during aging. Current interests include cell-cell interactions, junctional complexes, and epidermal aging.

Laboratory of Behavioral Sciences—Dr. Bernard T. Engel

- Psychophysiology Section—Dr. Bernard T. Engel

This laboratory is primarily concerned with the application of behavioral and psychological techniques and principles to the control or mediation of physiological responses. There are both clinical research programs in the area of behavioral medicine, and basic research programs using animal models to study neural control of cardiovascular function, as well as central neurotransmitter changes with age.

- Learning and Problem Solving Section—Dr. David L. Arenberg

This section investigates the effects of aging on motor behavior, perceptual skills, learning, memory, problem solving ability, and personality characteristics. Laboratory facilities exist to measure cognitive and perceptual function in man, in addition to learning and motor behavior in rodents (including selected inbred strains of mice).

- Stress and Coping Section—Dr. Paul Costa

Investigators in this section examine personality and its influence on the aging individual's ability and efforts to adapt to problems of adult life. Research focuses on coping mechanisms which adults have developed to deal with such stresses as physical declines and illness, retirement, or widowhood. Longitudinal analysis is used to establish long-range predictors of coping success or failure.

Laboratory of Cellular and Molecular Biology—Dr. Gunther L. Eichhorn

This laboratory conducts research basic to the aging process at the cellular and molecular levels, with emphasis on genetic information transfer and environmental effects.

- Inorganic Biochemistry Section—Dr. Gunther L. Eichhorn

This section studies the effects of metal ions on nucleic acid structure and on genetic information transfer, including chromatin structure, RNA synthesis, and protein synthesis. It is primarily concerned with the mechanisms of introducing error into genetic information transfer. Studies are made of age changes in the structure of chromatin and ribosomes.

- Macromolecular Chemistry Section—Dr. Josef Pitha

Scientists in this section study the interaction of cells with synthetic macromolecules. Investigators probe age changes on the cell surface with specially designed macromolecules and also synthesize potential polymeric drugs. Investigations are also conducted on age-dependent physicochemical alterations of chromatin and its transcription and on the production of abnormal proteins synthesized during the aging process.

Laboratory on Molecular Aging—Dr. Bertram Sacktor

In this laboratory, highly qualified associates have the opportunity to develop expertise qualifying them for careers in basic medical research. The thrusts of the biochemical, biophysical, and physiological programs are directed toward the biology of membranes and cells in culture, as it impacts on renal, intestinal, cardiac, and parotid gland functions. The problems and questions studied relate to: the molecular organization of the membrane; the mechanisms of vectorial ion and non-electrolyte transport; the hormonal regulation of transport systems, including reception, transduction, and propagation of stimuli mediated via cyclic nucleotides, calcium dependent proteins, and vitamin D_3; the isolation of carriers and reconstruction of functional synthetic membranes; the turnover of membranes; and the failure to maintain

membrane structure and function with age which leads to physiologic dysfunction and cell death.

Laboratory of Neurosciences—Dr. Stanley I. Rapoport

This laboratory investigates the function, structure, physiology, biochemistry and pharmacology of the central and peripheral nervous systems and of muscle, and the changes that take place during development and aging in animal models and in man. Investigators are studying the ultrastructure, transport, and permeability at the blood-brain barrier, blood-ocular barriers, and peripheral nerves; experimental modification of barrier permeability; regional cerebral metabolism and blood flow in relation to brain function; neuropharmacology in relation to stress, hypertension, and synaptic transmission; neurophysiology of nerve, muscle, and synapses; factors regulating neuronal death and neuron-neuron and neuron-effector organ interaction; and neuro-endocrinology. The basic program is coordinated with the clinical research program on cerebral metabolism in aging and dementia.

National Institute of Child Health and Human Development

Norman Kretchmer, M.D.,
Director
James B. Sidbury, M.D.
Scientific Director
D. Lynn Loriaux, M.D., Ph.D.,
Acting Clinical Director

Clinical Associates

The National Institute of Child Health and Human Development offers eight clinical associate positions each year. Appointments are for 2 or 3 years, depending on the program chosen.

The Endocrinology and Reproduction Research Program selects two or three associates yearly. Applicants should be Board eligible in internal medicine or obstetrics and gynecology prior to the initiation of the associateship. Internists participate in the Combined Endocrinology Training Program of the NIH, which leads to Board eligibility in the subspecialty of endocrinology and metabolism. Obstetrics and gynecology associates participate in a combined gynecology-endocrinology fellowship with the NIH, Walter Reed Army Hospital and National Naval Medical Center, which leads to Board eligibility in gynecologic endocrinology. Appointments are generally made 2 years in advance of the starting date of the fellowship.

For the Pediatric Medical Program, applicants should preferably have completed PL-3 level training by the time of entry. Earlier entry will also be considered. The components of the program include endocrinology, nutrition, metabolism, biochemical genetics, and developmental gastroenterology. The first year includes ward responsibilities.

In both the Endocrine and Pediatric Programs, the clinical associate will identify the preceptor and laboratory in which he or she will do research during the first 2 months. The associate may elect to work in any of the laboratories of the NICHD Intramural Research Program.

Research Associates

Research associates will work in one of the basic science laboratories.

Clinical Research Branches

Neonatal and Pediatric Medicine Branch—Dr. J. B. Sidbury

Research is conducted on the diagnosis, treatment, and fundamental mechanisms of diseases of infants and children. Emphasized are the inborn errors of metabolism, nutritional abnormalities, developmental and physiologic aspects of intestinal cells, congenital malformations, and endocrine disturbances of children.

- Section on Development Biology and Clinical Nutrition—Dr. James W. Hansen

This section conducts research in nutrition, developmental endocrinology, and mineral metabolism in infants and children. The program involves detailed study of calcium, magnesium, and trace element kinetics and metabolism in children and laboratory animals, including nonhuman primates.

- Section on Human Biochemical and Developmental Genetics—Dr. Joseph D. Schulman

Various inborn errors of metabolism, especially disorders affecting the sulfur amino acids, are investigated. This section seeks to improve understanding of the molecular basis of these diseases. Metabolism of amino acids, amino acid transport, and developmental biochemistry are also areas of investigation.

- Section on Developmental Gastroenterology and Nutrition—Dr. Norman Kretchmer

The purpose of this section is to study the differentiation of the intestinal crypt cell. Elucidation of the mechanisms of intestinal proliferation may aid in the understanding of malabsorption states.

Endocrinology and Reproduction Research Branch—Dr. Kevin J. Catt

This branch conducts an integrated program of clinical, biochemical, and biologic studies pertinent to endocrinology and reproductive biology.

- Section on Hormonal Regulation—Dr. Kevin J. Catt

Emphasis is placed on the binding and effects of polypeptide hormones such as gonadotropins and angiotensin. Major concerns include the characterization and isolation of membrane receptors and analysis of the receptor-second messenger systems.

- Section on Meolecular Endocrinology—Dr. Maria Dufau

This group investigates the molecular basis of peptide hormone action, with particular emphasis on the control of gonadal and adrenal function; analyzes the nature of gonadotropin receptors and activation of steroid biosynthesis in testis and ovary; and investigates the properties and biological activity of circulating gonadotropins in physiological regulation and clinical disorders of pituitary and gonadal function.

- Section on Biophysical Endocrinology—Dr. David Rodbard

The section performs mathematical and statistical analysis of endocrine regulatory processes and the physical properties of protein hormones studied by polyacrylamide gel electrophoresis; applies mathematical modeling, computer simulation and biophysical methods to studies on hormone-receptor interaction and regulation of the ovarian cycle; and investigates cardiovascular changes in thyroid disease.

- Section on Molecular Structure—Dr. Erhard Gross

Research is done on the analysis and synthesis of peptides with unique

structural features. Correlations between structure and biologic activity are analyzed in hypothalamic-releasing factors, chemotactic and ion-channel-forming peptides, and peptides causing fetal resorption and inhibition of tumor growth.

Developmental Endocrinology Branch—Dr. Lynn Loriaux

The endocrine concomitants of growth, development, and differentiation are examined. Current laboratory investigations include studies of the mechanism and control of steroid biosynthesis, secretion, transport and target tissue action. Of particular clinical interest are disorders of adrenal function, male and female infertility, and disorders of puberty and secondary sexual development.

Three clinical associates are accepted each year. During the first year, the associate rotates among the endocrinology branches of the NIH to gain a broad knowledge of clinical endocrinology. The next 2 years are spent primarily in laboratory investigation in collaboration with a senior investigator in any laboratory of the Institute.

Pregnancy Research Branch—Dr. Gary D. Hodgen

Interests of this branch range from the physiology of pregnancy, the identification of genetic and developmental factors which contribute to perinatal fetal and maternal morbidity and mortality, through fertility regulation and toxicological aspects of ovarian function to fertilization and implantation. These studies employ a variety of animal models, as well as laboratory aspects of clinical investigation. Obstetrics and gynecology associates selected for the national fellowship in reproductive medicine will rotate among gynecologic and obstetrical endocrinology programs at NIH, Walter Reed Army Hospital, and the National Naval Medical Center during the first year. The next 2 years are spent primarily in laboratory investigation in collaboration with a senior investigator.

- Section on Endocrinology—Dr. Gary D. Hodgen

Basic research is conducted in reproductive endocrinology and in laboratory aspects of clinical investigation. Major emphasis is placed on nonhuman primates for studies of ovarian function and pregnancy and on the physiology and chemistry of gonadotropins.

Social and Behavioral Sciences Branch—Dr. Leon J. Yarrow

This branch engages in research on cognitive, social, and motivational development. Studies in progress have concentrated on the first year of life. Current investigations are concerned with methodologic and theoretical issues regarding early environmental influences, the assessment of neonatal characteristics, the measurement of mastery behavior during infancy, and the emergence of the special bond between mother, infant and father.

Research Laboratories

Laboratory of Developmental Neurobiology—Dr. Philip G. Nelson

The neurobiologic basis for short- and long-term interaction between nerve cells is studied electrophysiologically and biochemically. The central neural mechanism underlying sensory discrimination in primates is studied by electrophysiologic and behavioral techniques. Combined molecular and behavioral methods are used in the analysis of experiential modifications of brain function.

- Section on Brain and Behavior—Dr. David Symmes

Electrophysiologic correlates of sensory coding and discriminative behavior are analyzed with microelectrode computer techniques. The focus of interest is in vocal communi-

cation among subhuman primates and its possible relationships to human speech.

- Section on Functional Neurochemistry—Dr. Harold Gainer

Emphasis is on the analysis of biochemical changes in identified neurons associated with electrophysiologic and behavioral alterations. Specific neuronal protein synthesis and axoplasmic transport, glial-neuronal interactions, pacemaker activity, and neural peptides are studied.

- The Section on Intermediary Metabolism—Dr. Gordon Guroff

This section is studying the mechanism of action of enzymes of neurochemical interest, the biosynthesis and degradation of macromolecules in neural tissue, and the mechanism of action of nerve growth factor. Other studies concern the evaluation of the effects of excesses or deficiencies of intermediary metabolites on cellular differentiation.

- Section on Neurobiology—Dr. Phillip G. Nelson

Tissue-cultured neural and muscle tissue and small *in vitro* vertebrate and invertebrate neural systems are studied electrophysiologically and biochemically. Long-term interactions between neurons and between nerve and muscle are of particular interest.

- Section on Neuroendocrinology—Dr. David C. Klein

Research activities involve environmental, pharmacologic, developmental and biochemical factors critical to the metabolism and function of the pineal gland. Current studies on this model of neural and neuroendocrine regulation focus on the molecular mechanism involved in the transsynaptic adrenergic cAMP regulation of gene expression. In addition, control of reproductive physiology by the pineal gland is investigated.

Laboratory of Molecular Genetics—Dr. Philip Leder

This laboratory consists of a group of scientists using the tools of molecular and cellular biology to answer questions about differentiation, development, and the control of genetic functions in simple and complex organisms. The range of model systems under investigation includes bacterial and animal viruses, tumor cells, embryonic lens tissue, as well as the differentiating hematopoietic and immune organ systems. Techniques employed range from bacterial, viral, and cell culture methods to gene isolation and recombinant DNA technology.

- Section on Gene Organization and Control—Dr. Philip Leder
- Section on Molecular Regulation—Dr. Michael Cashel
- Section on Molecular Structure—Dr. Jacob V. Maizel, Jr.
- Section on Cellular Differentiation—Dr. Joram Piatigorsky
- Section on Microbial Genetics—Dr. Robert Weisberg
- Section on Animal Viruses—Dr. Heiner Westphal

Developmental Pharmacology Branch—Dr. Daniel W. Nebert

The molecular mechanisms underlying genetic differences and environmental factors affecting drug metabolism are investigated. Interests of the branch span from biophysical characterization of membrane-bound and cytosolic enzymes, to the use of mammalian model systems, especially the inbred mouse and rat, to projects in clinical pharmacology.

- Section on Pharmacogenetics and Molecular Teratology—Dr. Daniel W. Nebert

Studies are concerned with the development of methods *in vitro* and in cell culture for the assessment and prediction of the teratogenic, toxic, mutagenic, or carcinogenic effects of exogenous or endogenous compounds in animal model systems and in man. Developmental curves and the expression of genes controlling drug-metabolizing enzymes are studied, and the transplacental inducing effect of drugs, chemical carcinogens, mu-

tagens and other environmental pollutants are investigated as possibly important factors in the etiology of birth defects.

National Institute of Dental Research

David B. Scott, D.D.S.,
Director
Marie U. Nylen, D.D.S.,
Director, Intramural Research
Dr. Karl-Åke Omnell, D.D.S., Odont. D.,
Clinical Director

The National Institute of Dental Research recruits about one clinical associate, two clinical dental associates, and two research associates each year. Assignments are for 2 years and are generally not extended. Appointments usually begin on July 1. Selection of candidates for clinical associate and clinical dental associate positions is based on program needs and qualifications of candidate. The chiefs of branches and sections screen applications, carry out personal interviews of candidates, and make recommendations to the clinical director, who will make final selection. Selection of candidates for research associate positions will be made following personal interviews by chiefs of laboratories and branches who have vacancies occurring within their programs. After results of matching are announced, each successful candidate is asked to confirm acceptance of the position.

The clinical and basic research program areas and the names of the program chiefs are listed below. A brief sketch of the clinical research areas is provided. Prospective applicants desiring more information should write to Dr. Marie U. Nylen, Director of Intramural Research, NIDR, National Institutes of Health, Bethesda, MD 20205.

Clinical Associates

The clinical associate is assigned to one of the clinical research programs within which he or she carries out both clinical and laboratory studies. In addition, the clinical associate is responsible for performing the medical evaluation and followup of all patients admitted to the Dental Clinic under one of the Institute's research protocols. One year of internship and at least 1 year of residency should be completed before the appointment begins.

Clinical Dental Associates

Clinical dental associates are assigned to clinical research programs where they spend approximately 60 percent of their time. The remainder of the time is spent providing dental services in the Dental Clinic. One year of internship and at least 1 year of additional clinical experience are desirable before appointment begins.

Research Associates

Research associates are assigned to one of the basic research laboratories or branches where they devote all their time to participating in laboratory research. One year of internship and at least 1 year of residency should be completed before the appointment begins.

Clinical Research Branches

Clinical Investigations Branch—Dr. Richard L. Webber

Investigations are directed toward research and development of noninvasive diagnostic techniques, and analysis of the functional development of the oral and pharyngeal region. Specific emphasis is placed on radiologic and other noninvasive analysis techniques.

- Diagnostic Methodology Section—Dr. Richard L. Webber

Interdisciplinary investigation linking clinical expertise with technical competence to facilitate a systems approach to diagnostic problems is the focus of this section's work. Diagnostic systems are designed, modeled, and evaluated with the use of digital simulation techniques. Prototype systems are then developed and tested clinically. Bases for improvement include matching of system elements, image enhancement and new geometric bases or quantitative analysis of tissue morphology.

- Oral and Pharyngeal Development Section—Dr. James F. Bosma

Studies of the development of the oral and pharyngeal tissues emphasize the relationship between form and function. This work includes clinical evaluation of sensory and motor development in normal individuals and patients of all ages with aberrant functions. Specific projects are concerned with the biochemistry of salivary constituents and psychophysical measurement of functional changes in taste.

Neurobiology and Anesthesiology Branch—Dr. Ronald Dubner

- Neural Mechanisms Section—Dr. Ronald Dubner

Research on peripheral and central nervous system mechanisms of oral-facial sensation is done by this laboratory. The primary objective is to correlate behavioral responses to thermal stimuli with neuronal activity at various levels of the trigeminal system. Research activities include: correlated behavioral and electrophysiological studies of responses to noxious and innocuous thermal stimuli in nucleus caudalis, the trigeminal homolog of the spinal dorsal horn; neurophysiological studies of the organization of the upper layers of the spinal cord dorsal horn; and psychophysical studies of experimental and clinical pain assessment with the use of verbal descriptor and metric analog scales of various dimensions of the pain experience in humans.

- Neurocytology and Experimental Anatomy Section—Dr. Stephen Gobel

This section uses a variety of anatomical approaches to study how noxious inputs which are transmitted by primary trigeminal neurons are processed in the central nervous system. Major efforts are directed at the study of the morphology, synaptic connections and development of second order interneurons and projection neurons in the dorsal horn of the medulla (trigeminal nucleus caudalis) as well as the identification of the major sources of brain stem descending inputs to these neurons. In addition, a series of experiments are being conducted in which tooth pulps are being removed in experimental animals in order to consider how the destruction of pulpal nerve endings

consequent to dental disease alters the neural circuitry in trigeminal pain pathways.

• Anesthesiology Section—Dr. Ronald Dubner

Clinical research on the development and application of sedative agents and techniques used in the control of anxiety and apprehension in dental patients is done here. Research includes physiological, pharmacological and psychological studies of the efficacy and toxicity of combinations of intravenous sedative drugs used in extensive oral surgery procedures.

National Caries Program Caries Prevention and Research Branch
—Dr. William H. Bowen

• Community Programs Section
—Dr. Herschel Horowitz

• Etiology Section—Dr. Horace M. Stiles

• Biometry Section—Janet Brunelle

This branch investigates the etiology and prevention of dental caries. Particular attention is paid to the factors which influence formation of dental plaque. Emphasis is also placed on the natural defense mechanisms in the mouth, particularly as they relate to dental caries. Epidemiological studies of low caries communities are done. Clinical trials of caries preventive agents and research into better methods of data analysis are also carried out.

• Dental Services Section—Dr. Karl-Åke Omnell

This section conducts clinical research and provides consultations and care for the NIH patient population.

Basic Research Laboratories

Laboratory of Biochemistry—Dr. Karl A. Piez

• Section on Protein Chemistry—Dr. Karl A. Piez

The emphasis of the program is on the chemistry and structure of collagen, elastin and other proteins. Biochemical and biophysical methods including high resolution electron microscopy, nuclear magnetic resonance spectroscopy, laser light scattering, and computer modeling are extensively used.

• Section on Enzyme Chemistry
—Dr. John E. Folk

Enzymes called transglutaminases stabilize biological structures (such as the fibrin clot) by introducing covalent cross-links. Studies in this section are directed toward elucidating the mechanism of action and the biological significance of these enzymes.

• Section on Proteoglycan Chemistry—Dr. Vincent C. Hascall

Proteoglycans constitute a diverse group of connective tissue macromolecules consisting of both carbohydrate and protein. Their chemistry, structure, biosynthesis and biological role are being investigated using organ and cell culture systems.

Laboratory of Biological Structure
—Dr. Arthur R. Hand

• Experimental Morphology Section—Dr. Arthur R. Hand

• Molecular Structure Section—Dr. Edward D. Eanes

The laboratory conducts basic research on the structural and chemical organization of the hard and soft tissues of the oral cavity. Major emphasis is directed toward elucidation of the chemical, physical and biological mechanisms responsible for the differentiation, growth and mineralization of bones and teeth. Other studies are concerned with the structure and function of exocrine secretory cells and the basic mechanisms of cellular secretion. Current investigations include: the structure, formation and maturation of calcium phosphate salts; characterization of the matrix proteins of enamel and dentin and their interactions with the mineral

phase; factors regulating the differentiation and growth of endochondral bone and bone cell-matrix interactions; and glycoprotein transport and packaging and membrane dynamics in secretary cells.

Laboratory of Developmental Biology and Anomalies—Dr. George R. Martin

- Connective Tissue Section—Dr. George R. Martin
- Craniofacial Development Section—Dr. Robert M. Pratt

Research is directed toward the elucidation of teratogen-induced and inherited malformations. Projects include studying molecular mechanisms of cellular development migration and tissue formation and interaction. Drugs are used to probe these steps. Their effects are studied at the light and electron microscope level. Alterations in the production of such macromolecules as glycoproteins, collagen, and proteoglycans are also studied. Studies on the effects on the transcription of genes and the translation of mRNA are underway. Our emphasis is on normal, mutant, fetal and malignant cells from bone, cartilage and other connective tissues. Associates in this laboratory are encouraged to pioneer new research areas.

Laboratory of Microbiology and Immunology—Dr. Stephen E. Mergenhagen

- Clinical Immunology Section—Dr. Reuben P. Siraganian

This group is involved in clinical studies on the role of host factors in periodontal diseases, autoimmune diseases and allergic disorders. Particular emphasis is given to inflammatory mediators released from lymphocytes, basophils and mast cells and their relationship to clinical disease. Considerable opportunity exists for collaboration with other scientists in the basic science components of the laboratory.

- Microbiology Section—Dr. Charles Wittenberger

Clinical research activities now in progress assess the potential of phase-contrast microscopy and videotape recordings in identifying bacterial complexes found in healthy and diseased gingival crevices and pockets. These methods are also used to determine the effect of oral hygiene agents and methods on pathogenic bacterial complexes. Video displays or twin viewing of bacterial fields are used to teach patients about the pathogenesis and control of periodontal diseases, which presents opportunities for studying new methods of patient education and assessing various information delivery systems. Other studies deal with oral bacteria implicated in periodontal lesions and the prevalence of resistant strains of oral bacteria in patients undergoing antibiotic therapy. The genetic mechanism involved in this acquired resistance is also being investigated.

Laboratory of Oral Medicine—Dr. Abner Notkins

The laboratory conducts clinical research on diseases of the oral cavity. The interdisciplinary program emphasizes virology, oncology, and endocrinology. Present research projects focus on factors responsible for recurrent and persistent viral infections such as herpes viruses; cellular immunity in viral infections; interferon and immediate hypersensitivity reactions; virus-induced immunopathology; the etiology of various dermatologic disorders including aphthous ulcers; the role of viruses and other factors in diseases of the exocrine gland (Sjögren's syndrome, pancreatitis, salivary gland tumors) and endocrine glands (diabetes mellitus); and double-blind clinical trials to evaluate the effectiveness of various drugs in the treatment of oral lesions.

National Institute of Environmental Health Sciences

David P. Rall, M.D., Ph.D.,
Director

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to identify the chemical, physical and biologic factors in the environment that can adversely affect man; to contribute to an understanding of the mechanisms and manifestations of human diseases produced by these agents; and to provide the scientific basis for the development of control measures by other agencies. NIEHS is particularly concerned with the effects of agents at low concentrations acting over long periods, the interaction of multiple agents resulting in enhanced effects, and the modifying effects of variable physical and biologic states within man on the susceptibility to and course of disease induced by these agents.

The headquarters and intramural research programs of NIEHS are located at Research Triangle Park, North Carolina. NIEHS is the only one of the 11 Institutes comprising the National Institutes of Health located away from the campus in Bethesda, Maryland.

Proximity to three universities—the University of North Carolina at Chapel Hill, Duke University of Durham, and North Carolina State at Raleigh—has encouraged the development of a close working relationship between the staffs of the universities and the Institute. This relationship affords the NIEHS staff access to extensive library facilities as well as opportunities to participate in teaching, seminars, and other scientific and professional activities associated with the universities.

Staff Associates

Staff associates work at NIEHS under the direction of Dr. David Rall, Director, and a laboratory or branch chief in the Institute. Each associate will work directly under a senior scientist in an area of research chosen by the associate and the Institute. The initial appointment is for 2 years. These appointments are designed to give highly qualified physicians an opportunity to improve their backgrounds for careers in basic medical research. NIEHS does not have clinical facilities; however, associates may work out informal arrangements with the clinical staff at the University of North Carolina and/or Duke University Medical School. Prospective applicants desiring more information should write to the Scientific Director, NIEHS, P.O. Box 12233, Research Triangle Park, North Carolina 27709.

Basic Research Laboratories

Laboratory of Pharmacology—Dr. James R. Fouts

The toxic effects of low-level and/or chronic exposure to environmental constituents or contaminants on mammals and marine species are studied in this laboratory. Interactions (on or within the animal) of these environmental factors with each other and with drugs are also studied. Pro-

jects currently underway include: toxication-detoxication systems in the liver, lung, and skin and effects of pollutants on these systems and the balance between toxication and detoxication reactions; age-related changes in toxication-detoxication systems in various organs; uptake, storage, metabolism, and release of chemicals in the lung and liver; species differences in xenobiotic disposition and metabolism; and studies on the formation and metabolism of reactive metabolites of hydrocarbons in various marine species and purification and comparison of components of toxication-detoxication systems in various organs.

Laboratory of Biochemical Genetics—Dr. Heinrich V. Malling

Research is focused on the monitoring of somatic mutations in peripheral blood cells and skin fibroblasts and on the detection and measurement of germinal mutations with the use of electrophoretic serum protein variants.

Laboratory of Reproductive and Developmental Toxicology—Dr. Robert L. Dixon

Scientific efforts are directed toward the understanding of mechanisms of toxicity. Special emphasis is placed on the following tasks: determine mechanisms of teratogenesis with *in vivo* and *in vitro* techniques to develop more rapid and economical laboratory methods to predict birth defects; assess environmental agents for their teratology potential; study the molecular mechanisms underlying cellular differentiation; evaluate perinatal aspects of enzymology, endocrinology, and pharmacokinetics with regard to environmental toxicity; understand the effects of prenatal exposure to hormonally active environmental agents on the development of reproductive tract function; determine the possible gestational origin of subtle toxic effects that do not become apparent until later in life; define the effect of environmental agents on oogenesis and spermatogenesis; and develop preclinical predictors of toxicity with the use of *in vitro* cells and tissues, lower animals, and biochemical test systems.

Laboratory of Behavioral and Neurological Toxicology—Dr. Clifford L. Mitchell

Research is concerned with the study of changes in behavior and neurologic function produced by long-term exposure to low levels of many chemical and physical agents present in the environment. Special consideration is being given to the identification of laboratory procedures useful in assessing the role of environmental factors in the development of behavioral and neurologic abnormalities, studies concerning the mechanisms whereby environmental factors produce behavioral and neurotoxic effects, and studies concerning the conditions that predispose individuals to the behavioral and neurotoxic effects of environmental factors.

Laboratory of Pulmonary Function and Toxicology—Dr. Paul Nettesheim

The long-range objectives of this laboratory are to obtain through animal studies information needed to provide the scientific basis for the prevention of respiratory diseases which might have an environmental etiology. The intramural program is studying mechanisms of pulmonary biology and pathology in appropriate experimental models. Research is being pursued in pulmonary endocrinology, prostaglandins, biochemical pathology, environmental carcinogenesis, pulmonary cell biology, and pulmonary pathology.

Biometry Branch—Dr. David G. Hoel

This branch provides biometric support for the NIEHS program by employing mathematical and statistical techniques to determine the biologic effects of chemical, physical and biologic agents present in the environment. This is accomplished by incorporating statistical principles of experimental design, sampling, and

data analysis for laboratory and epidemiologic studies and mathematical analyses of biologic systems into Institute programs. Mathematical and statistical procedures are applied and, when necessary, developed to determine the distribution of and estimate the rates of environmentally related diseases among populations, to test hypotheses and to study the interactions of environmental agents from multifactor laboratory experiments. The branch develops mathematical models for describing and predicting biologic responses to environmental agents. The branch also provides computer support that ranges from the development of information retrieval and inventory maintenance systems to the simulation of complex biologic models. To accomplish the mission of the Biometry Branch, the following areas of activity are identified: analytical statistics, epidemiology, mathematical statistics, biomathematics and risk assessment computer programming, and data processing.

Laboratory of Environmental Biophysics—Dr. Colin F. Chignell

This laboratory is involved in several studies on the biologic effects of physical factors in man's environment. At present, the programs concentrate on biologic effects of microwave radiation and noise singly and in combination with other factors. The effects of microwaves on reproduction and nerve functions (isolated nerves and activities of the central nervous system as reflected in behavior) are under study. Noise effects on various inner ear functions are being studied in combination with ototoxic drugs and heavy metals. New methods have been developed for quantifying microwave doses and for studying sound effects on inner ear physiology and biochemistry. Sophisticated spectroscopic techniques are used to study the molecular interaction of environmental agents with biologic systems.

Environmental Biology Branch—Dr. John A. Moore

Collaborative support laboratories are maintained in the disciplines of inhalation toxicology, comparative pathology, immunology, and veterinary medicine, and research appropriate to the functions of branch laboratories is planned and conducted. Current programs include studies on the effect of environmental chemicals on immune competence and pulmonary structure and function; and characterization of the toxic effects of the chlorinated dibenzodioxins, dibenzofurans, and polychlorinated biphenyls.

Laboratory of Environmental Chemistry—Dr. James D. McKinney

This branch supports research programs and collaborates with Institute laboratories on studies on the chemistry of suspect environmental agents. The branch utilizes, develops, and improves analytical methodology for specified agents which includes immunoassay and instrumental methods such as mass and magnetic resonance spectrometric techniques and high pressure liquid chromatography. Suspect environmental agents and their conversion products are synthesized and characterized. Research studies on environmental agents, biological materials and their metabolites emphasize biomechanism elucidation.

Laboratory of Animal Genetics—Dr. Burke Judd

This laboratory concentrates on studies on the genetic structure of populations and on the structural and functional organization of higher eukaryotic genes, using model systems such as Drosophila and cultured mammalian cells. A group in genetic enzymology seeks to develop rapid and efficient methods for the purification of specific macromolecules, proteins, and nucleic acids. One project in chemical genetics focuses on the analysis of mutant mammalian proteins and DNA using primary sequence analysis.

Laboratory of Molecular Genetics—Dr. John W. Drake

Research in this laboratory is concerned with the chemical nature of the mutation process, especially the nature of the initial damage to or spontaneous alteration of DNA and its subsequent enzymatic processing. Genetic and biochemical analyses are used with both prokaryotic systems and model eukaryotic systems such as yeasts and cultured mammalian cells. The laboratory also provides general services for other laboratories such as prokaryotic chromosome mechanics, including recombinant DNA and strain synthesis. Studies aimed at developing or improving microbial screening systems for detection of chemical mutagens are also pursued.

Laboratory of Biochemical Genetics—Dr. Heinrich V. Malling

This laboratory is concerned with studying mechanisms for induction of mutations in mammalian cells *in vivo* and *in vitro;* development and validation of test systems for detecting mutations in both mammalian somatic and germinal cells; correlating mutation induction with physiologic and biochemical endpoints, and ultimately, facilitating evaluation of risks of exposure of human populations to environmental mutagens. Research is done on characterizing markers for mutation, such as monospecific fluorescent antibodies for mutant hemoglobin and mutant enzymes in sperm, and refining and validating automated systems, such as the cell sorter for monitoring mutations in larger numbers of samples.

Laboratory of Organ Function and Toxicology—Dr. George W. Lucier

This program provides a research focus for investigation of the effects of environmental agents on renal, hepatic, and gastrointestinal function. Special emphasis is placed on conducting studies to elucidate the mechanisms by which environmental agents alter normal functions of these organ systems including the role of metabolism, endocrine factors, and toxicant-receptor interactions; and conducting studies to identify sensitive indicators of organ specific toxicity useful for prediction and early detection of toxicity in experimental animals and humans.

National Institute of General Medical Sciences

Ruth L. Kirschstein, M.D.
Director

Sara A. Gardner, Ph.D.,
Director, Pharmacology
Research Associate Program

Pharmacology Research Associates

The National Institute of General Medical Sciences (NIGMS) has 11 positions available each year for pharmacology research associates. Those who are appointed begin on July 1 and are offered 2 years of postdoctoral training in a laboratory of a participating Institute of NIH under the Pharmacology Research Associate Program. The program seeks to develop leaders in pharamacology research for key positions in academic, industrial, and governmental research laboratories.

The program is directed to those persons who have already made a commitment in pharmacology by training or research in the field.

Associates will do research relating principles of pharmacological sciences to contemporary biomedical problems. Training in such areas as applied mathematics, biometrics, organic chemistry, biochemistry, physics, and instrumentation is also

available. During their tenure, pharmacology research associates devote the larger portion of their time to laboratory research in the biomedical sciences, with no routine clinical responsibilities.

Professional growth is achieved through the process of personal guidance by senior NIH scientists who are preceptors. A variety of laboratory problems and research approaches are designed to advance the work in progress and the competence of the prospective independent investigator. Preceptors and research associates are matched by a mutual selection procedure after personal interviews.

Associate candidates include those who will have received either the Ph.D., M.D., or equivalent degree and have research experience in areas relevant to pharmacology. They may also include those with research experience in a related area but who wish to further their development in pharmacology. Candidates for an M.D. degree may use this opportunity to further their training in basic pharmacologic research in preparation for a career in clinical pharmacology or a related dsicipline. Many NIH Institutes participate in the Pharmacology Research Associate Program.

Clinical Pharmacology

A program is available for research training specifically in the area of clinical pharmacology. Applicants for research training in clinical pharmacology should have the M.D. degree, a minimum of 1 year, preferably 2, of graduate medical training (internship, residency), and a demonstrated interest in clinical pharmacology. The successful applicant will participate in a developing 2-year program under the guidance of several groups of investigators who are actively engaged in clinical pharmacological research in the Clinical Center, NIH. These preceptors will include but are not limited to:

Dr. Donald Calne, Clinical Director, National Institute of Neurological and Communicative Disorders and Stroke

Dr. Bruce Chabner, Chief, Biomedical Pharmacology Section, National Cancer Institute

Dr. Michael Ebert, Chief, Section on Experimental Therapeutics, National Institute of Mental Health

Dr. Stephen Epstein, Chief, Cardiology Branch, National Heart, Lung, and Blood Institute

Dr. James Gillette, Chief, Laboratory of Chemical Pharmacology, National Heart, Lung, and Blood Institute

Dr. Frederick Goodwin, Chief, Clinical Psychobiology Branch, National Institute of Mental Health

Dr. Harry Keiser, Clinical Director, National Heart, Lung, and Blood Institute

Dr. Irwin Kopin, Chief, Laboratory of Clinical Science, National Institute of Mental Health

Dr. Daniel Nebert, Chief, Developmental Pharmacology Branch, National Institute of Child Health and Human Development

Dr. Judith Rapoport, Medical Officer, Unit on Childhood Mental Illness, Biological Psychiatry Branch, National Institute of Mental Health

Dr. Snorri S. Thorgeirsson, Head, Biochemical Pharmacology Section, National Cancer Institute

Dr. William Z. Potter, intramural clinical pharmacologist, will serve as coordinator of the associate's overall training in clinical pharmacology. The program emphasizes laboratory methods applicable to pharmacological research in man but also includes training in general clinical pharmacological principles (clinical pharmacokinetics and pharmacodynamics,

biostatistics, drug evaluation, drug epidemiology, etc.).

The clinical pharmacology associate's research experiences will be planned individually to meet the needs dictated by previous training, experience, and career goals. This research experience will involve both laboratory and clinical investigation.

A training plan, including formal course work, for each associate will be developed by the Pharmacology Research Associate Advisory Committee and the associate. Formal course work may be waived with the concurrence of the Pharmacology Research Associate Advisory Committee. A series of seminars will be organized with the participation of the clinical pharmacology associates to insure that their needs are met. The associates will also help develop and instruct in the medical student elective program in clinical pharmacology.

In addition to a primary involvement in clinical pharamacological research, the associate will participate in clinical pharmacology rounds. These rounds will be directed on an alternating basis by preceptors from the different categorical areas to insure a broad exposure to a wide range of problems in clinical pharmacology. Part of the clinical pharmacology experience will be collaborating with the coordinator in clinical pharmacology consultations for the Clinical Center.

An applicant may be considered for both the regular Pharmacology Research Associate Program and the clinical pharmacology option. Further information may be obtained from the Pharmacology Research Associate Program, NIGMS, Westwood Building, Room 919, 5333 Westbard Avenue, NIH, Bethesda, MD 20205.

Program Areas

Choice of program area depends upon the candidate's previous training and career plans. Those who have already received adequate graduate training or conducted meritorious research in pharmacology may request as a preceptor any senior scientist at the NIH, with the approval of the Pharmacology Research Associate Advisory Committee. Since the objective of this program is to offer postdoctoral training opportunities to those interested in pursuing a research career in pharmacology, applicants without training or experience in pharmacology should select program areas which will provide such opportunities. The Pharmacology Research Associate Advisory Committee offers counseling to applicants invited to the NIH for interviews.

National Cancer Institute

Laboratory of Chemical Pharmacology—Dr. Richard H. Adamson

The general areas being studied include the physiologic disposition of antitumor agents; the structure-activity relationship of antitumor agents; new approaches to cancer chemotherapy and therapeutics in general, including studies on polymers and on the nature of drug receptors; comparative pharmacology; and the induction of tumors in nonhuman primates with carcinogens and/or viruses and chemotherapy of these tumors.

- Pharmacokinetics and Pharmacodynamics Section—Dr. Daniel S. Zaharko

This section is involved with pharmacologic investigations of cancer chemotherapeutic agents. Research efforts are currently directed toward altering the selectivity of known anticancer drugs by linking them to synthetic polymers and by using them in conjunction with normal intermediary metabolites such as nucleosides, amino acids, or vitamins. Most studies are carried out in rodent species

and involve pharmacokinetics, radioactive tracers, *in vitro* enzyme inhibition, and tumor growth inhibition.

The research interests of this section are the relationship between pharmacokinetics and drug effects, the biochemical selectivity of anticancer agents in different organs and tissues; and the transport and role of nucleosides in the biochemical balance of the whole animal.

• Section on Biochemical Pharmacology—Dr. Snorri S. Thorgeirsson

Investigations are conducted on the relationship between mutagenic and carcinogenic effects of drugs and foreign compounds, with emphasis on antitumor agents; the mechanism of chemically induced cancer, with major emphasis on metabolic activation of chemical carcinogens and the genetic control of tumor initiation; cell differentiation—the mechanism of transformation (viral and chemical) and the "redifferentiation" of already transformed cells with potentially therapeutic agents; and clinical pharmacology, with emphasis on pharmacokinetics, antitumor agents, and drug toxicity.

Clinical Pharmacology Branch—Dr. Bruce A. Chabner

Mechanisms of tissue toxicity caused by adriamycin: This laboratory has recently proposed that adriamycin cardiotoxicity results from free radical generation during drug metabolism. The group is examining the endogenous defenses of cardiac tissue against free radical damage to see what role they might play in the clinical pattern of cardiotoxicity. The laboratory is also engaged in the design of a clinical trial to test the ability of various free radical scavengers such as vitamin E to ablate adriamycin cardiac toxicity.

Molecular pharmacology of antitumor agents: These studies are directed at understanding the quantitative and qualitative interactions of antitumor agents with target sites in tumor cells. Emphasis is on understanding factors which determine response to antifolates, 5-fluorouracil, and the pineal hormone, melatonin, at the cellular and biochemical level. *In vitro* uptake, binding to receptor sites, and cytotoxicity of these agents are examined in tissue culture systems as well as in the whole animal.

Laboratory of Medicinal Chemistry and Biology—Dr. David G. Johns

This laboratory conducts an integrated program for the rational development of antitumor agents; carries out the synthesis of compounds with potential antitumor activity; and assesses the effects of such agents on experimental tumor systems *in vitro* and *in vivo* and on a variety of potential subcellular target sites—nucleic acids, cell membranes, and microtubular protein and enzyme systems. Of special concern are agents that act as "stoichiometric" or "titrating" enzyme inhibitors, with current emphasis on the interaction of 2′-deoxycoformycin with adenosine deaminase and on the biochemical and pharmacologic effects of 2′-deoxycoformycin when used in combination with adenosine analogues. Another area of current interest is the maytansine group of mitotic inhibitors and the nature of their binding with microtubular protein.

Laboratory of Medicinal Chemistry and Biology—Dr. Marco Rabinovitz

Attention is focused on the development of approaches for the potentiation of cancer chemotherapeutic activities. Nutritional and pharmacologic regimens are first explored in tissue culture and then extended to the tumor-bearing animal in attempts to direct cytotoxic agents toward the tumor cell and away from sensitive normal tissues. New cytotoxic and potentiating agents are also synthesized to achieve this goal. Biochemical studies include the analysis of inhibition kinetics of binding, transport and detoxification of cytotoxic agents in sensitive and resistant tumor cells

and in sensitive host tissues. An investigator is encouraged to use several of the above methodologies in pursuit of the solution to a particular problem.

Laboratory of Toxicology, Medicinal Chemistry, and Biology—Dr. Anthony M. Guarino

- Drug Interactions Section—Dr. Theodore Gram

Research interests include the chemical and biochemical mechanisms involved in interactions between xenobiotics and biologic materials that result in toxic responses; the morphologic reaction to toxic response to determine if the morphologic alterations precede, coincide with, or follow toxicity; studies to determine whether toxicity is spontaneously reversible and what factors, if any, augment or diminish the toxicity; and investigations on whether toxicity exhibits organ specificity and, if so, how it might be explained.

The Section on Drug Interactions is particularly interested in the role of drug oxidation and conjugation in the detoxification and toxication of xenobiotics. Past work has been oriented toward microsomal and cytosol enzymes of the liver, lung, and kidney in these phenomena. Studies with lung have been conducted in intact animals, the isolated perfused lung, slices from normal lung and lung tumors, tissue homogenates, and subcellular fractions. This group is also interested in the functions that tissue uptake, binding, metabolism, and clearance have in drug-related specific end-organ toxicity. Investigations are currently in progress to evaluate these questions since they relate to the serious and dose-limiting problems of pulmonary fibrosis associated with a number of oncolytic agents such as bleomycin, renal necrosis resulting from platinum compounds, and myocardial fibrosis associated with adriamycin.

National Heart, Lung, and Blood Institute

Cardiology Branch—Dr. Stephen E. Epstein

The branch's research objectives are oriented primarily toward an elucidation of the physiological and biochemical mechanisms responsible for control of both the normal and failing heart, as well as the effects of various pharmacological interventions on the normal and failing heart. Projects include pharmacological, physiological, and biochemical studies in man and animals. Major emphasis is on the study of the mechanisms responsible for myocardial cell-death in acute myocardial infarction and interventions designed to decrease ischemic injury (by altering proteolysis, prostaglandin production). Emphasis is also placed on study of the biochemical mechanisms involved in actin-myosin interaction and in muscle contraction.

Laboratory of Chemistry—Dr. Henry M. Fales

- Section on Physiological Chemistry—Dr. John J. Pisano

Normal and pathologic states in man are studied at the molecular level. Under investigation are neuroactive (enkephalins) and vasoactive peptides (bradykinin and angiotensin), precursor proteins of the peptides (kininogens), and the enzymes (kallikreins) involved in their biosynthesis and degradation. Modern analytic techniques such as gas chromatography, high-performance liquid chromatography, affinity chromatography, mass spectrometry, and radioimmunoassay are commonly employed. Research is currently directed toward the study of hypertension, new factors regulating coagulation and fibrinolysis, micromethods for the detection and amino acid sequence analysis of polypeptides, and the discovery of naturally occurring biologically active peptides with a variety of bioassay techniques.

Laboratory of Chemical Pharmacology—Dr. James R. Gillette

• Section on Drug-Enzyme Interaction—Dr. James R. Gillette

Various aspects of drug disposition are investigated, including the relationship between drug metabolism and drug toxicity. The main objective of this section has been the elucidation of the mechanisms of drug metabolism by enzyme systems in liver microsomes, the factors that control the activity of these systems, and the importance of these enzymes in converting inert substances to alkylating agents and other biologically active metabolites. This group also studies ways of extrapolating data obtained with liver microsomes to the cellular and animal level.

Hypertension-Endocrine Branch—

• Section on Biochemical Pharmacology—Dr. Walter Lovenberg

Research is directed toward understanding the regulation of monoaminergic systems and the relationship of these systems to specific diseases. Both biochemical and pharmacological approaches are used to investigate various neuronal systems and how information is transmitted between cells. This group is particularly interested in the role of cyclic nucleotides and calcium in these receptor mediated responses. Some of the current research projects are: molecular characterization of the monoamine biosynthetic enzymes; regulation of catecholamine and serotonin synthesis by protein phosphorylation reactions; molecular events involved in the transduction of nerve impulses into changes in target cell proteins and enyzme levels in small blood vessels and the pineal gland; the distribution and physiologic role of the hydroxylase cofactor (tetrahydrobiopterin); the role of calmodulin in regulation of the activity of neuronal systems; the biochemical mechanism of antihypertensive and antipsychotic drugs, and the role of central and peripheral nervous systems in the regulation of blood pressure in experimental animals and man. The work encompasses several fields including pharmacology, enzymology, protein chemistry and molecular biology.

Laboratory of Biochemical Genetics—Dr. Marshall W. Nirenberg

• Section on Molecular Biology—Dr. Marshall W. Nirenberg

Studies are conducted on clonal cells derived from the nervous system, including those of normal and neoplastic origin as well as somatic cell hybrids. The objectives of this section are to identify molecules and reactions that enable cells to communicate with each other and to investigate the problem of how genes determine synaptic circuits when neurons are assembled into circuits during embryonic development. Work predominantly involves biochemistry and enzymology, mammalian cell culture, cyclic nucleotide enzymology, cell receptors, and enzymes of neurotransmitter metabolism.

Research is also directed toward the mechanism of action of opiate peptides, dependence and tolerance to these compounds, and the relationship of opiate receptors in the regulation of adenylate cyclase activity.

• Section on Macromolecules—Alan Peterkofsky, Ph.D.

This section is concentrating on studies of cellular control mechanisms. One area of interest involves a study of the hypothalamic tripeptide, thyrotropin-releasing factor. The biochemical and pharmacological properties of a newly discovered metabolite of thyrotropin-releasing factor are under investigation. These experiments may lead to a better definition of the metabolism and mechanism of action of this hormone. Another focus of attention is the control of the synthesis and metabolism of cyclic nucleotides in bacterial cells. Current information suggests that cyclic AMP concentrations in *Escherichia coli* are controlled by cellular metabolites by a mechanism similar in some respects to that by which hormones affect cyclic AMP levels in many mammalian cells.

Laboratory of Cellular Metabolism—Dr. Martha Vaughan

The laboratory works on problems related to the control of cyclic nucleotide synthesis and degradation and the mechanisms of action of hormones and other agents that influence these processes in mammalian cells. Research in progress deals with cell-surface receptors, adenylate and guanylate cyclases (particularly activation of the former by cholera toxin), and several cyclic nucleotide phosphodiesterases that differ in their regulatory properties.

- Section on Cellular Pharmacology —Dr. Michael A. Beaven

This section has an interest in the study of drug action of the cellular level. Current work includes: studies on the mechanism of repression of cell proliferation and lymphocyte blast transformation by anti-inflammatory drugs; the inhibition of white cell recruitment and chemotaxis in inflammatory reactions by anti-inflammatory drugs; and release and metabolism of histamine and other active factors during inflammatory and allergic reactions. Collaborative studies are underway with purified populations of histamine-containing and parietal cells from the gastric mucosa. The response of these cells to endogenous mediators and drugs and their localization in the gastric mucosa are currently being investigated.

National Institute of Arthritis, Metabolism, and Digestive Diseases

Laboratory of Bioorganic Chemistry—Dr. Bernhard Witkop

- Section on Pharmacodynamics —Dr. John W. Daly

This section is engaged in research on the formation, degradation, and role of cyclic nucleotides in the nervous system—mechanisms that control adenylate cyclase and phosphodiesterases, receptors for catecholamines and other neurotransmitters, the relationship of membrane potential and generation of cyclic nucleotides, the interrelationship of adenosine and calcium in the regulation of cyclic nucleotide formation and action, morphologic entities associated with cyclic nucleotide formation and action, and the effect of toxins on neuronal function.

- Section on Pharmacodynamics—Phil Skolnick, Ph.D.

The research program is concerned with understanding the relationship between receptors for psychoactive compounds and the endogenous substances which normally subserve these receptors. The techniques employed in studying these relationships range from biochemical investigations of the nature of endogenous ligands and their interaction with membrane receptors to the use of both primary and transformed cell culture models and classical "whole animal" pharmacology. Specific projects currently under investigation include: (1) the development of new drugs to characterize multiple benzodiazepine receptor sites in mammalian CNS and to determine the functional role(s) of these receptors, (2) study of the role of purines in modulation of central function through interaction with benzodiazepine receptors, and (3) the physiologic and pharmacologic modulation of adrenergic receptors in the CNS and the relationship to the functional role(s) of such receptors.

- Section on Oxidation Mechanisms—Dr. Donald M. Jerina

The primary interest of this section is the elucidation of the fundamental mechanisms by which drugs and environmental chemicals are transformed in the body. In many instances oxidative metabolism produces chemically reactive metabolites which are responsible for the cyto-

toxic, mutagenic, and carcinogenic activity of the drug substrate. Recent studies have been concerned with the roles of the cytochrome P-450 system and epoxide hydrase in the formation of mutagenic and carcinogenic metabolites from the polycyclic aromatic hydrocarbons. Emphasis is on modern instrumental techniques such as high pressure liquid chromatography, high resolution mass spectrometry-gas chromatography, and high resolution magnetic resonance in the study of metabolism catalyzed by homogeneous enzymes.

Laboratory of Biochemical Pharmacology—A) Dr. Herbert Tabor

Work in this laboratory is mainly concerned with the biosynthesis, metabolism, and function of various polyamines (e.g., spermidine and spermine) and amino acids. The polyamines occur in large amounts in biologic materials and are important in stabilizing various cell components, such as cell membranes, ribosomes, and nucleic acids. Future work will be directed, in part, toward the mechanism and *in vivo* significance of these effects. The studies provide experience with a variety of techniques (enzyme characterization, bacteriophage, nucleic acid chemistry, and isotopic and nonisotopic synthesis). The amino acid studies are concerned with the induced enzymes involved in histidine degradation and their use as tools in studying induction, repression, and enzyme mechanisms.

Other work includes studies on control mechanisms for other enzymes in bacteria and in mammalian cell culture, mechanism of action of antibiotic agents, ribosome structure, and bacterial permeability.

Laboratory of Biochemical Pharmacology—B) Dr. Loretta Leive

This laboratory studies how structure is related to function in biological membranes. One area of study is the membrane of macrophages, for which we use macrophage cell lines. Mutants altered in membrane properties such as adhesion, phagocytosis, and interaction with externally added effectors are being isolated, and the accompanying membrane changes will be analyzed. Other mutants resistant to known surface agents, such as lectins, will be selected, and the effect of such resistance on the above properties will be studied. The aim is to elucidate the biochemical mechanism of the metabolically important processes of adhesion, phagocytosis, and interaction with effectors. Another area of study is the outer membrane of gram-negative bacteria. This membrane is unusual in its permeability, as it admits small hydrophilic molecules but excludes larger hydrophobic ones, which is the opposite of most known biological membranes. Its exclusion of hydrophobic molecules accounts for much of the resistance of gram-negative bacteria to antibiotics that attack gram-positive organisms. Mutants altered in outer membrane components, or with increased permeability, are being used to analyze the mechanisms involved. The results may suggest ways of increasing drug sensitivity in gram-negative organisms.

Laboratory of Biochemistry and Metabolism—Dr. William B. Jakoby

This group approaches the problems of detoxification at the level of purified enzymes. Proteins brought to the stage of homogeneity are studied with respect to physical, binding, and regulatory properties. Emphasis is on the mechanism of action. Current work is directed at those enzymes catalyzing reaction with glutathione, those effective in methylation, and those participating in sulfate conjugation.

Clinical Hematology Branch— Dr. Harvey B. Pollard

The primary interest of this group is in mechanisms of secretion of proteins, hormones, and transmitters from neuroendocrine and other cells. Critical problems which are under investigation include how calcium acts

to fuse secretory vesicles to plasma membranes, and how release of vesicle contents during exocytosis subsequently occurs. The approach of this laboratory is to search for special proteins that could mediate such events; at present these include synexin, a protein that fuses secretory vesicle membranes exclusively in the presence of calcium, and various secretory vesicle membrane proteins and enzymes. The interactions of these and related proteins with a wide variety of pharmacologic and environmental agents known to affect secretory processes are being analyzed.

Diabetes Branch—Dr. Jesse Roth

The Diabetes Branch studies receptors for peptide hormones, especially insulin, insulin-like growth factors, and growth hormone. Current projects are focused on biological regulation of receptor affinity and number; the role of receptors in hormone and drug action at the target cell; receptors in disease states, especially disorders of glucose metabolism; isolation and purification of the insulin receptor; insulin and insulin receptors in the central nervous system; anti-receptor antibodies; morphological correlates of hormone binding to receptor (electron microscopy and immunocytochemistry); receptors on circulating cells and cells in tissue culture (normal and transformed). The clinical service of the Diabetes Branch provides continuous access to patients with receptor-related disorders.

National Institute of Child Health and Human Development

Laboratory of Developmental Neurobiology—Dr. Phillip G. Nelson

Research is conducted in neurobiology with the use of tissue cultures of normal and neoplastic nerve and muscle and various invertebrate preparations. The analysis of the membrane mechanisms of action of neurotransmitters and other neuroactive compounds is a primary aim. A number of biochemical studies of long-term interneuronal interactions related to synaptogenesis are in progress. Biosynthesis and processing of a number of peptides of neurobiologic importance and the membrane mechanism of action of such peptides are under investigation. A primate vocal communication system in the squirrel monkey is being analyzed in behavioral and etiologic terms and with neurophysiologic techniques. Biochemical studies of inductive mechanisms in the nervous system are being done with the pineal gland and sympathetic ganglia.

- Section on Neuroendocrinology—Dr. David C. Klein

Investigations within the section focus on the molecular mechanisms through which hormones and biogenic amines regulate gene expression, with the primary experimental model being cultured pineal cells. Research is concerned with the relationship between biogenic amines and the production and release of hormones; emphasis is given to the study of β-adrenergic receptor control of cyclic AMP. In addition, enzyme induction is studied using drugs as biochemical and electrophysiological tools to understand the intracellular reactions involved in large changes in enzyme activity, and the effects of neurotransmitters. A second major area of interest is the factors regulating circadian rhythms; current investigations are concerned with the central neural mechanisms involved in generating daily rhythms in primates.

Developmental Pharmacology Branch—Dr. Daniel W. Nebert

This branch investigates the molecular mechanisms underlying genetic differences and environmental factors influencing drug metabolism in man. The program includes a search to understand congenital malformations; the toxic, mutagenic, or carcinogenic effect of drugs; the de-

velopment of drug-metabolizing enzymes and their capacity to be induced or repressed; and jaundice caused by breast-milk feeding. Genetics in mice and cell culture techniques are commonly used as experimental model systems. With these techniques, this group is attempting to distinguish genetic factors from environmental influences and to develop methods for assessing or predicting a compound's teratogenic, toxic, mutagenic, or carcinogenic effect in man. This research complements and supports the ongoing Institute program in the Pregnancy Research Branch and the Neonatal and Pediatric Medicine Branch.

National Institute of Environmental Health Sciences

This Institute is the only one of the 11 Institutes that comprise the National Institutes of Health that is not situated on the campus in Bethesda, Maryland. It is located in Research Triangle Park, North Carolina.

Laboratory of Environmental Biophysics—Dr. Colin F. Chignell

Research programs of the laboratory cover two main areas—the biological effects of some of the physical factors (nonionizing radiation, noise, light) present in the environment and the use of physicochemical techniques to monitor the interaction of chemical and physical agents with various biological systems. The aim of the nonionizing radiation program is to develop new microwave exposure systems and to determine the effect of microwave exposure on human health. Current efforts include the effect of microwave radiation on the central nervous system and animal behavior, the cardiovascular system, the immunologic defense systems and the fetus. The major effort of the noise program is directed towards elucidating basic mechanisms of noise-induced hearing loss, providing better methods for assessing such losses and providing the means for accurately reproducing specific noise exposure environments. The remainder of the effort is focused on the reproductive, teratogenic, cardiovascular and behavioral effects of noise. The light program is concerned with the mechanism of chemically induced photosensitivity and photoallergy. The effect of light of different wavelengths on the behavior and response of experimental animals to chemical agents is also being examined. The program in molecular biophysics mainly focuses on the use of sophisticated spectroscopic techniques (ESR, NMR, fluorescence and absorption spectroscopy, CD) to monitor the interaction of environmental agents with biologic systems. Current studies include the generation of free-radical intermediates during this metabolism of xenobiotics, the mechanism of mast cell degranulation, the binding of dyes to nucleic acids, and the interaction of metal ions with proteins and membranes.

Laboratory of Pharmacology—James R. Fouts, Ph.D.

Toxication/detoxication systems—Systems are compared among organs and across species, especially those systems involved in production and detoxication of reactive metabolites of environmental pollutants (e.g., epoxides). The ontogeny of systems in selected tissues and species and the role of toxication/detoxication in cytotoxicity, mutagenesis, teratogenesis, and carcinogenesis are studied. Purification of selected systems is done for comparisons between tissues and species and for studies of mechanisms. Immunochemical techniques are used for localization of selected toxication/detoxication systems in tissue slices, in isolated cells from various tissues, or in culture. Selected cell populations are isolated form tissues for study of toxication/detoxication systems—e.g., in Clara or type II

cells of lung. Studies in isolated perfused organs (e.g., lung, liver) of relationships between chemical uptake, metabolism, excretion and tissue toxicity are also done.

Marine aquatic pharmacology/physiology—Mechanisms of accumulation, biotransformation, excretion and toxicity in vertebrates and invertebrate aquatic species are studied. Selected xenobiotic metabolizing systems from aquatic animals are purified, characterized and compared with similar enzyme systems from mammals. Aquatic species and their xenobiotic metabolism as sentinel systems for selected waterborne pollutants are studied. Field laboratories are located in Maine and Florida.

Laboratory of Reproductive and Developmental Toxicology—Dr. Robert L. Dixon

Scientific efforts are directed toward the understanding of mechanisms of reproductive, endocrinologic, and developmental toxicity. Special emphasis is placed on the following tasks: determine mechanisms of teratogenesis using *in vivo* and *in vitro* techniques to develop more rapid and economical laboratory methods to predict birth defects; assess environmental agents for their teratogenic potential; determine the molecular mechanisms underlying cellular differentiation; study the molecular basis and determine the effects of environmental agents on endocrine function; understand the effects of prenatal exposure to hormonally active environmental agents on the development of reproductive tract function; determine the possible gestational origin of subtle toxic effects which do not become apparent until later in life; define the effect of environmental agents on oogenesis and spermatogenesis; and develop preclinical predictors of reproductive, endocrinologic, and developmental toxicity using *in vitro* cells and tissues, lower animals, and biochemical test systems.

Laboratory of Behavioral and Neurological Toxicology—Dr. Clifford L. Mitchell

The research programs of the Laboratory of Behavioral and Neurological Toxicology cover three broad areas—the identification of laboratory procedures useful in assessing the role of environmental factors in the development of behavioral and neurological abnormalities, studies concerning the mechanism whereby environmental factors produce their behavioral and neurotoxic effects, and studies concerning the conditions which alter the responsiveness of individuals to the behavioral and neurological effects of environmental factors. An interdisciplinary approach to these problems is taken utilizing behavioral, neurochemical, neurophysiological, and neuropathological techniques. Particular emphasis is placed on the behavioral and neurological effects resulting from exposure to environmental agents during the development of the nervous system. Among the substances being studied are heavy metals, halogenated hydrocarbons, volatile solvents, microwaves, and their interactions with psychoactive drugs.

Laboratory of Pulmonary Function and Toxicology—Dr. Paul Nettesheim

The research programs of the Laboratory of Pulmonary Function and Toxicology are concerned with the study of the cellular and biochemical basis of normal and abnormal lung functions. Special areas of emphasis are: (1) endocrinological aspects of lung cell biology, the role of neuroendocrine cells in the lungs, their relationship to some hormonally active pulmonary neoplasms, and mast cell hormones; (2) metabolism of prostaglandins in the lungs and the effect of prostaglandins on some metabolic functions of the lung; (3) the composition, secretion, and function of the noncellular alveolar lining layer, particularly its protein components, and disturbances of the acellular alveolar

lining layer in disease; (4) the biology, life cycle and function of respiratory tract epithelial cells studied using *in vivo* and *in vitro* techniques; (5) the mechanisms of toxicity of airborne particles and fibers on lung tissues and the mechanisms of toxicity of asbestos studied *in vivo* and *in vitro;* and (6) mechanisms of respiratory tract carcinogenesis, the development of neoplastic disease, *in vitro* epithelial cell transformation and promotion studies, and mechanisms of co-carcinogenesis and promotion.

National Institute of Mental Health

Laboratory of Clinical Science—

• Section on Pharamacology—Dr. Julius Axelrod

The section engages in several areas of research related to biochemical pharmacology. These include studies on development of methods for the measurement of hormones, biogenic amines, and enzymes; the distribution and metabolism of hormones, and the isolation and characterization of enzymes involved in hormone and biogenic amine metabolism. The laboratory also engages in examining control mechanisms of the biochemistry of the pineal gland, methylation reactions and membrane structure and function.

• Section on Histopharmacology —Dr. David M. Jacobowitz

This section studies monoaminergic nerves (noradrenergic, dopaminergic, serotonergic), cholinergic and gabaminergic neurons in the brain, and the peripheral autonomic nervous system. A major aim of this section is to study the basis of behavioral regulation by a multidisciplinary approach to central neurotransmitter systems. Histochemical and neurochemical analyses are carried out at the level of discrete central nuclei and pathways in order to define the underlying basis for behavioral changes. Catecholamine histofluorescence, immunofluorescence, drugs, stress, and surgical stereotaxic lesions are used to correlate changes in neuronal function with various parameters of behavior. Neuronal amines, enzymes and peptides are measured within specific brain nuclei, tracts and other discrete regions of the brain using a microdissection method and radioisotopic assays. Immunofluorescence methods are also being used to study the localization of enzymes (DβH) and peptides (α-MSH, bombesin, enkephalin, substance P) in the brain.

• Section on Medicine—Dr. Irwin J. Kopin

The research efforts of this section are centered around the study of biochemical and physiologic effects of drugs and toxins that alter the formation, disposition, metabolism, and receptor interaction of putative neurotransmitters and the enzymes that control their synthesis in the central and peripheral nervous systems. The techniques used include radioisotopic methods (*in vivo* and *in vitro*), tissue slices, perfused organs, and organ and tissue cultures. Brain lesions and chronic indwelling catheters placed in arteries, veins, and cerebral ventricles are used in studies on animals. For application to clinical studies, procedures are developed to evaluate neurotransmitter and neuroendocrine function in human subjects with various neuropsychiatric disorders or during administration of psychoactive drugs. Plasma, urine, and cerebrospinal fluid are analyzed for various drugs, amines, and metabolites, and the rates of utilization or synthesis determined using radioimmunologic, enzymatic, or mass spectroscopic techniques.

• Unit on Neuroendocrinology—Dr. Michael J. Brownstein

The members of this unit are trying to locate peptidergic neurons

in the CNS and to characterize them anatomically. In addition, this unit wants to learn how peptidergic neurons synthesize, transport, store, and release their biologically active products and hopes to show how these processes are regulated by hormones and neurotransmitters.

Laboratory of Cerebral Metabolism—Dr. Louis Sokoloff

- Section on Developmental Neurochemistry—Dr. Louis Sokoloff

Laboratory investigations are directed toward the biochemical aspects of growth, development, maturation, and regulation of metabolism in the CNS. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry to whole-animal physiology. Present emphasis is on the applications of a method recently developed in this laboratory that permits measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiologic and pathologic states.

Laboratory of Preclinical Pharmacology—Dr. Erminio Costa

This laboratory conducts a program of research in neurochemical pharmacology directed to elucidate the molecular mechanisms that regulate production, metabolism and action of various putative neurotransmitters and the mode of action of various psychoactive drugs. Current research includes: the molecular regulation of postjunctional receptors for catecholamines, serotonin, GABA, acetylcholine and polypeptides; the modification of the interactions between the neurotransmitters and endorphins and other polypeptides elicited by long-term treatment with drugs; the use of stable isotopes to measure the turnover rate of acetylcholine, norepinephrine, dopamine, serotonin and GABA by mass fragmentography in brain nuclei; the study of the mechanisms involved in the transsynaptic regulation of gene expression in neural cells; and the study of the heterogeneity of polypeptide neuromodulators in central and peripheral stores as an approach to understanding the regulation of their dynamic equilibrium.

- Section on Biochemical Pharmacology—Dr. Norton H. Neff

The concern of this section is with the effect of drugs on the biochemistry and physiology of the nervous system. Emphasis is placed on the biogenic amine-containing neuron. Current studies are directed toward the characterization of enzymes involved in amine metabolism, the biochemical evaluation of receptor responses, the evaluation of the mechanism of action of drugs that alter neuronal function, and the possible role of the biogenic amines in various disease states.

Laboratory of Neurochemistry—Dr. Seymour Kaufman

The main effort of this laboratory is devoted to the study of the metabolic interaction between the brain and its peripheral environment. The current focus is on the enzymes in the brain that function in the biosynthesis of neurotransmitters such as dopamine, norepinephrine, and serotonin. Various experimental interventions that can affect this dynamic central-peripheral interaction—including disease states (phenylketonuria, hepatic coma, and infections), dietary changes, hormones, and drugs—are being investigated and analyzed at the molecular level.

Also being studied is the regulation in brain and other tissues of the biosynthesis of tetrahydrobiopterin, the essential pterin cofactor for the enzymes that hydroxylate phenylalanine, tyrosine and tryptophan.

Laboratory of General and Comparative Biochemistry—Dr. Werner A. Klee

The major emphasis of the current program is directed toward the elucidation of the mechanism of action of opiates and the peptides that nor-

mally interact with opiate receptors. Included are studies on the isolation and characterization of opiate receptors and endogenous morphine-like factors and the regulation of adenylate cyclase activity by opiate receptors. These studies, carried out primarily with purified systems and neuronal cells in tissue culture, are aimed at understanding narcotic tolerance and dependence as well as analgesia and euphoria in biochemical terms. The relevance of this work to the action of other CNS-active drugs and to normal brain function is also being explored.

Biological Psychiatry Branch

• Section on Biochemistry and Pharmacology—Dr. John F. Tallman

Current investigations are directed toward an understanding of the regulation and actions of receptors at the cellular level. Two examples of current work are: interactions between GABA receptors and benzodiazepine receptors and the synergistic actions of these receptors on neuronal firing and biochemical parameters of cellular activity; and mechanisms which control the number and functioning of β-adrenergic receptors in cultured cell lines and alterations in β-adrenergic receptors which occur following exposure of cells to β-adrenergic agonists (desensitization).

• Section on Biochemistry and Pharmacology—Dr. Agu Pert

This laboratory is concerned with analyzing the mechanisms of action of psychoactive drugs and neuropeptides in the brain and defining the neurochemical coding of brain circuits which control specific behaviors. Extracellular single-cell recording as well as iontophoretic techniques are employed to evaluate the actions of drugs in specific brain regions. Lesion and microinjection procedures are then utilized to relate these effects to behavior. Our current emphasis is on two projects: the actions of endorphins and enkephalins on brain function especially the processing of pain information, and the effects of lithium (a therapeutic agent in manic-depressive illness) on neurotransmitter receptor sensitivity.

• Section on Biochemistry and Pharmacology—Dr. Candace B. Pert

The recent structural identifications of substance P and enkephalin have spurred our investigations of other neuropeptides (bombesin and vasointestinal peptide). Our primary interest is the characterization of receptors for neuropeptides and other psychoactive substances whose mechanism of action is currently unknown. Mapping the distribution of brain receptors (by *in vitro* autoradiography) currently with their endogenous ligands (by immunohistofluorescence) provides clues for elucidating interneuronal connections. Physiological and/or pathological states which greatly elevate plasma and/or cerebrospinal fluid levels of neuropeptides are sought to provide clues about normal function. Direct receptor binding techniques provide an approach for sorting out receptor heterogeneity on the basis of association with GTP-sensitive regulatory units, specific ionic effects related to receptor-coupled ionophores, and relative agonist or antagonist affinity.

Clinical Psychobiology Branch

—Dr. Frederick K. Goodwin

Clinical pharmacology, investigation into the neurotransmitter and neuroendocrine related mechanisms involved in primary affective disorders (bipolar and unipolar depression) and basic research on brain proteins, peptides and receptors are major parts of an integrated effort in the psychobiology branch. In the unit on Clinical Pharmacology (Dr. William Potter) double-blind drug trials are used to compare clinical response, neuroendocrine changes, drug pharmacokinetics, and measures of amine turnover and metabolism. Methodologies include rating of clinical change, determinations of hormone concentrations by radioimmunoassay, measurements of drugs and monoamine

metabolites with gas chromatography or gas chromatography-mass spectroscopy, and use of tracer doses of radiolabeled drugs and amine precursors in man.

Isolation and chemical-biological characterization of brain proteins and peptides are performed in the laboratory. The Unit on Preclinical Pharmacology (Dr. Steven Paul) has a special interest in the characterization of brain receptors, the identification of endogenous ligands, and the pharmacological and physiological effects of ligands.

A metabolic inpatient unit and an outpatient drug treatment clinic provide the opportunity for longitudinal studies of clinical and biochemical changes. In addition, research is directed toward answering practical questions in therapeutics such as the use of loading doses to predict the ultimate steady-state therapeutic concentration of tricyclic antidepressants, and the use of biological and clinical measures as predictors of therapeutic response to specific drugs.

National Institute on Alcohol Abuse and Alcoholism

Laboratory of Preclinical Studies—Dr. Forrest F. Weight

Research investigations in this laboratory center around the pharmacology of neurons and synapses in the central and peripheral nervous system. The general areas studied include: cellular actions of neurotransmitters such as dopamine, acetylcholine, serotonin and GABA; membrane mechanisms of neurotransmitters and drug actions; cellular actions of enkephalins, endorphins and peptides; identification of neurotransmitters in central synaptic pathways; and mechanisms of action of ethanol, barbiturates, opiates and other neuroactive substances. The research techniques available to a research associate include: extracellular unit recording and iontophoresis of drugs and putative transmitters to single neurons in the CNS; intracellular recording and intracellular injection techniques; use of *in vitro* preparations such as CNS slices and sympathetic ganglia for studying the ionic basis of drug and transmitter action; sucrose gap recording for studying the pharmacology of drug-receptor interactions; and voltage clamp recording for studying the ionic basis of membrane permeability changes involved in drug and transmitter actions.

National Institute of Neurological and Communicative Disorders and Stroke

Experimental Therapeutics Branch—Dr. Donald B. Calne

Drugs are investigated as potential therapeutic agents in patients with motor disorders in whom central neuropathology has led to identifiable changes in transmitter function. Drugs are also used as tools to analyze the pharmacologic disturbances accompanying neurologic disorders. Blood, urine, and cerebrospinal fluid are assayed for alteration in the concentrations of transmitters or their metabolites.

Patients with severe seizure disorders are evaluated by several new techniques. A team of neurologists is involved, for example, in the study of the efficacy and metabolism of such drugs as sodium valproate. Drug interaction studies, the intensive analysis of different seizure types, including complex partial seizures, and studies on the application of positron emission tomography in epilepsy are underway.

Extracellular single-unit recording procedures are employed for the determination of drug effects on identified neurotransmitter systems in animals. Currently these studies

are focused on interactions between the substantia nigra and basal ganglia and on the sites and mechanisms of action of dopamine agonists and other agents thought to interact with neural function in these regions.

• Biochemical Neuropharmacology Unit—Dr. John W. Kebabian

The Biochemical Neuropharmacology Unit studies the biochemical mechanisms underlying the activity of receptors of neurotransmitters. There is a special interest for dopamine receptors found in brain and simpler peripheral endocrine tissues. In the simple endocrine tissues, it is possible to apply the knowledge of the biochemical mechanisms underlying receptor activity (especially in terms of cyclic AMP formation) to studies of physiological function of the tissue such as hormone release.

Laboratory of Neurophysiology—Drs. Jeffery L. Barker and Thomas G. Smith, Jr.

The principal aims of this laboratory are to understand how nerve cells communicate and how CNS-active drugs alter neuronal communications. The preparations used include the mammalian CNS grown in tissue culture and amphibian and molluscan nervous systems studied *in vitro*. The methods used are primarily electrophysiological, including intracellular recording, voltage-clamp techniques, and extracellular microiontophoresis. Specific projects include the comparison of neurotransmitter and peptide neurohormone functions at the single-cell and defined-circuit level; the cellular pharmacology of general anesthetics, convulsants, and anticonvulsants; and optical techniques applied to the analysis of neuronal function.

Neurotoxicology—Dr. Ellen K. Silbergeld

This group conducts basic research on environmental toxins, natural and synthetic, which, by their actions on the central and peripheral nervous systems, may cause neurologic disease. Research is directed towards elucidation of basic mechanisms of neurotoxin actions and development of correlations between cellular neurotoxicity and dysfunctions in behavior and biochemistry. Techniques used in this research include: behavioral pharmacology, neurochemistry (synaptic receptor binding and neurotransmitter turnover); quantitative electron microscopy; and anatomy. Current projects are on the use of neurotoxic agents to produce animal models of Huntington's disease and parkinsonism, and on the effects of artificial food colors and heavy metals on CNS functions and behavior.

National Institute of Mental Health

Herbert Pardes, M.D.,
Director
John C. Eberhart, Ph.D.,
Director, Intramural Research
Robert A. Cohen, M.D., Ph.D.,
Deputy Director

The National Institute of Mental Health (NIMH) offers an opportunity for postdoctoral research training in psychiatry and in the biologic and behavioral sciences. The NIMH Intramural Program is located on the NIH campus in Bethesda, Maryland, and in the William A. White Building, St. Elizabeths Hospital, Washington, D.C. Clinical associates conduct clinical and/or basic research, and are responsible for the clinical care of patients admitted for research and therapeutic purposes. Research associates

engage in laboratory research in the biologic or behavioral science laboratories under the preceptorship of the senior staff. All associates participate in tutorial seminars and other teaching programs as their needs and desires indicate. Lectures, seminars, and group discussion by members of the staff and by visiting lecturers complement the training program, making it possible for all associates to acquire a broad background in the neural and behavioral sciences with more intensive and individualized study in selected aspects of the field.

Clinical Associates

The NIMH recruits about 12 new clinical associates each year. Appointments normally begin July 1 and are usually for 2-year periods, although in some instances they may be extended.

Clinical associates usually begin their appointments at the completion of residency training. Exceptionally well-qualified individuals, however, may be appointed after 1 or 2 years of psychiatric training. The Clinical Center is approved for 1 year of psychiatric residency training at the PGY-4 level.

Applications for the Clinical Associate Program are now being accepted only for July 1982 appointments. Since selections for these positions will be made in the spring of 1981, PGY-2 or PGY-3 psychiatric residents may now apply.

Clinical associates usually work in close association with senior clinician-scientists on one of the clinical research wards or in a clinical research laboratory. The first year is usually predominantly clinical with intense experience in the diagnosis and inpatient management of research patients, special clinical and administrative issues in a research setting, psychopharmacology, clinical research methodologies and design (by the initiation of at least one clinical research project under the direction of the senior clinician-scientist), and the psychotherapy and psychodynamics of research patients and their families. The following years focus primarily on research that may be clinical, clinical-biochemical, or laboratory, depending on the interests of the associate and the status of the clinical research program. Intensive clinical supervision is available from senior psychiatrists and consulting psychoanalysts. Candidates desiring more information about clinical associate positions should write to Dr. J. Christian Gillin, NIMH, Building 10, Room 3N224, NIH, Bethesda, Maryland 20205.

Research Associates

Research associates work under the preceptorship of a senior staff scientist. They are usually assigned to a basic science laboratory for intense training and experience in specific neurobiologic or psychosocial concepts and methodologies. For further information about research associate positions in the neurobiologic area, contact Dr. Irwin Kopin, NIMH, Building 10, Room 2D46, NIH, Bethesda, Maryland 20205. For information in the psychosocial area, contact Dr. Marian Yarrow, NIMH, Building 15K, NIH, Bethesda, Maryland 20205.

Pharmacology Research Associates (PRAT)

Some of the NIMH programs participate in the PRAT program. These positions are provided by the National Institute of General Medical Sciences for special training in preclinical or clinical pharmacology. For more information about the PRAT program see pages 72 through 88.

Division of Clinical and Behavioral Research–
Dr. Robert A. Cohen

Biological Psychiatry Branch—Dr. William E. Bunney, Jr.

This branch conducts a broad program of research, training, and treatment of clinical psychiatric problems including schizophrenia, manic-depressive illness, drug abuse, and childhood mental illness. The focus of the branch is psychobiologic and brings together information from four disciplines—psychiatry, genetics, pharmacology, and biochemistry. Some specific research interests are psychogenetics, the biochemistry of neurotransmission, twins and siblings, investigations of perception and cognition, average evoked response, and studies of the physiology of sleep and sleep changes in psychiatric illness. A general goal of this branch is to develop programs to investigate biologic contributions to schizophrenia, manic-depressive illness, and childhood mental illness.

- Section on Neuropsychopharmacology—Dr. Daniel P. van Kammen

This 12-bed psychiatric research unit is involved in clinical and laboratory research on acute and chronic schizophrenia. The clinical associate will participate in and conduct studies concerning the pharmacologic, biochemical, phenomenologic, genetic and dynamic investigations of schizophrenia. Major current areas of interest involve the study of the role of dopamine and norepinephrine in schizophrenia and the use of drugs with specific actions on dopamine metabolism. Metabolites of neurotransmitters and enzymes are being assessed in the urine, plasma, and cerebrospinal fluid (CSF). Other areas of interest involve a multidisciplinary approach to schizophrenia, in collaboration with other investigators of NIMH and other Institutes; attempts to delineate vulnerability markers (state-independent and state-related variables); the prediction of antipsychotic drug response and prognosis; exploration of γ-aminobutyric acid, neuropeptides and neurotransmitter systems other than dopamine for their potential involvement in psychosis; evaluation of the antipsychotic effects of drugs such as propranolol and naltrexone; assessment of pharmacological and endocrinological aspects of the above-mentioned areas; plasmapheresis of schizophrenic patients; study of CATSCAN abnormalities; cognitive and psychophysiological evaluations and the yearly follow-up of discharged patients.

Clinical associates will be trained in research methodology, data analysis, clinical management of research patients and administration.

- Section on Psychogenetics—Dr. Elliot S. Gershon

A research goal of this section is to identify familially transmitted biologic and behavioral characteristics associated with the affective and other major psychiatric disorders, including pharmacogenetic and chromosome-linkage investigation. The section has a followup outpatient clinic for these studies. Other research goals are to identify the mode of genetic transmission, to separate out familial and nonfamilial factors in the liability to the disorders, to

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study in animal models the physiologic role and nature of inheritance of biologic and pharmacologic response characteristics of interest; and to develop mathematical models of inheritance appropriate to psychiatric disorders.

• Section on Psychobiology—Dr. Robert M. Post

This 12-bed psychiatric research unit focuses on the clinical and biologic assessment and treatment of patients with manic-depressive and schizoaffective illness and rapidly cycling phenomena. Clinical associates are research collaborators in a variety of studies of the interactions of psychological and biologic parameters in the psychoses and usually take responsibility for the design, conduction, and publication of several research projects. Mood, cognitive, and behavioral variables are viewed in relation to such biologic correlates as sleep, motor activity, evoked potentials, and endocrine function. Particular attention is given to the study in psychiatric patients of central amine metabolism with the use of CSF strategies such as the measurement of amine metabolites, electrolytes, cyclic nucleotides, regulatory enzymes, and peptides in CSF. Work is closely coordinated with several biochemical laboratories including one headed by Pauline Lerner. The mechanisms and time course of the biologic effects of psychotropic drugs are studied in relation to clinical response.

New pharmacologic agents are being tested, including dopamine receptor agonists, the anticonvulsant carbamazepine, and several endogenous polypeptides. The mechanisms underlying the paradoxic antidepressant effect of one night's sleep deprivation are being studied. Clinical and laboratory studies of psychomotor stimulants are ongoing. An active behavioral pharmacology laboratory is maintained for the study of the long-term effects of psychomotor stimulant administration and electrical kindling in rodents and primates as models for the development of psychosis.

• Unit on Sleep Studies—Drs. J. C. Gillin and R. J. Wyatt

This unit is studying the sleep patterns of the patients on the clinical research units. In addition to phenomena associated with various disorders, emphasis is placed on the biochemical substrates of sleep processes, the response of patients to various pharmacologic alterations, neuroendocrine relationships, and memory.

• Unit on Childhood Mental Illness—Dr. J. L. Rapoport

This unit operates on a four-bed day and/or overnight hospitalization inpatient program in collaboration with the Section on Experimental Therapeutics, Laboratory of Clinical Science and independently on a pediatric ward maintained by NICHD. Current focus is on diagnostic assessment and drug treatment of hyperactive children. Drug studies include pharmacokinetic studies of drugs given to children and studies of kinetics and metabolism of neurotransmitter systems via body fluids.

Also underway are outpatient studies of obsessive-compulsive and enuretic children and the evaluation of children whose parents have been hospitalized here in the past for affective illness.

• Unit on Studies of Drug Abuse —Dr. David Pickar

This is a program of inpatient evaluation on the research units of the clinical service. The Drug Abuse Unit is currently focusing on the problems of amphetamine as it represents a model psychosis for schizophrenia; the phenomenology, biochemistry and pharmacology of the experience of "high" in man; and central neurotransmitter metabolism.

Clinical Neuropharmacology Branch

—Dr. Dennis L. Murphy

The program is designed to contribute to the understanding of the

mechanisms of therapeutic drug effects in individuals with affective disorders, obsessive-compulsive symptoms and other behavioral disorders. The studies are primarily based on a 10-bed psychiatric research ward. An outpatient program with an emphasis on psychobiologic studies of possible high-risk segments of a community population complements the inpatient investigations.

Support for the clinical studies includes a behavioral assessment and data processing program as well as a biochemistry laboratory under the direction of Dr. Jonathan L. Costa. Facilities for small animal and nonhuman primate studies are also available in the Branch.

The ward research investigations, which are balanced between biologic-pharmacologic and psychological-phenomenologic approaches, take place in the setting of an active milieu treatment program. The incoming clinical associate, depending on his or her prior research and clinical experience, will usually participate at first in ongoing research projects and the clinical program. With increased experience, the clinical associate will work with a senior staff member in the planning, design, and implementation of one or more research projects to be initiated in the first year and completed in the second or possibly third year.

Emphasis is on the strategies and methods used in clinical research. Specific research projects range from psychological studies of the characteristics of individuals who do or do not respond to specific drugs, to laboratory or animal studies of the effects of drugs on cellular processes including enzyme activity, membrane transport and neurotransmitter receptor functions. Studies of psychoactive drug effects on neurotransmitter metabolism and neuroendocrine function are a particular focus in both the clinical and nonhuman primate areas.

Drugs currently under study include selective monoamine oxidase inhibitors, some natural precursors of brain neurotransmitters, and lithium carbonate, as well as some new investigational compounds. Special areas of study at present include drug response differences, neuroendocrine responses, and other characteristics differentiating subgroups of psychiatric patients; studies of platelet, plasma and brain amine oxidases; investigations of adaptational responses to longer-term drug administration in neurotransmitter receptors; the development of new electron microscope-based techniques (e.g. energy loss spectroscopy) for the study of the storage and metabolism of neurotransmitter amines and other substances in cells; and methods for the assessment of behavioral and psychological states.

Clinical Psychobiology Branch
—Dr. Frederick K. Goodwin

Clinical research is conducted in areas related primarily to affective illness (depression and mania) and its treatment. Laboratory research involves studies on the neurobiology of brain receptors, proteins, peptides, neurotransmitter amines, melatonin, and other neuroendocrine substances. Structurally the branch is divided into the Clinical Research Unit, the Unit on Neurochemistry and Preclinical Pharmacology, and the Outpatient and Follow-up Unit. Throughout the 2- to 3-year assignment, the associate's time is divided among clinical care-ward management, clinical research, and laboratory research, depending on interest. Direct responsibility for research projects is assumed in the beginning. The branch is also responsible for research training in clinical and preclinical pharmacology through the Pharmacology Research Associate Program of the National Institute of General Medical Sciences.

- Clinical Research Unit—
Dr. Thomas Wehr

This unit represents the major research resource of the branch and is located in a 15-bed psychiatric re-

search ward. Ongoing clinical projects include the following: under the direction of Dr. Philip Gold, neuroendocrine strategies for the evaluation of hypothalamic-pituitary function are developed, and these measures are integrated with the study of amine metabolites from spinal fluid and urine. Clinical studies of vasopressin function are a major current focus. A wide range of consultation and collaboration with endocrine groups in other Institutes is afforded by Dr. Gold's full participation in the Interinstitute Endocrine Program. Studies of biologic rhythms, under the direction of Dr. Wehr, involve the exploration of diurnal rhythms and longer term cycles; amine and melatonin rhythms are of special interest. State-dependent versus state-independent variables are evaluated in behavioral-biologic correlations. This unit studies the differential biochemical response to stress in depression-prone patients compared to normal individuals; the differential biochemical mechanisms of the acute versus prophylactic actions of lithium in manic-depressive patients; the efficacy of hormonal potentiation of antidepressant drugs; the biochemical identification of patient subgroups that predict drug response; and the interrelationship between drug action and the psychodynamics of manic and depressive patients. The clinical pharmacology of antidepressants, under Dr. William Potter, is a special interest, including the development of pharmacokinetic models for predicting dose.

- Units of Neurochemistry and Preclinical Pharmacology—Drs. Paul Marangos and Steven Paul

Methods for the assessment of urinary and spinal fluid amine metabolites are developed and maintained; in addition, immunoassays for hypothalamic peptides are under development. Animal studies are focused on the characterization, localization, and functional definition of neuron-specific protein, and mechanisms of psychotropic drugs are explored, particularly in relation to brain proteins, peptides, and neuronal receptor function. Exploration of an endogenous ligand for the diazepam receptor is one current focus. Primates are used in studies of biologic rhythms and the effects of drugs.

- Outpatient and Follow-Up Unit—Dr. Rex Cowdry and Mrs. Yolande Davenport

A short-term evaluation and treatment program for acute depression constitutes the major focus of the clinic, which is closely integrated with the inpatient unit. The clinic is also involved with the maintenance treatment and long-term evaluation of recurrent affective disorders. Studies of "well state" are integrated into prophylactic drug trials; the interaction between psychotherapy and drug therapy is a special interest.

A complete list of the branch's current research projects is available on request.

Laboratory of Clinical Science—Dr. Irwin J. Kopin

This program conducts research in biochemistry, pharmacology, physiology, medicine, and psychiatry, and the interrelationships between them. Applicants for the research associate program should have at least 1 year of clinical training, whereas clinical associates are required to have at least 2 years of postdoctoral training in neurology or psychiatry before arrival for duty. Parts of the program have been accredited for 1 year of training in psychiatry.

The research program objectives are attained through the cooperative efforts as well as the independent research of investigators in the various sections and units of the laboratory.

- Section on Pharmacology—Dr. Julius Axelrod

The section engages in several areas of research related to biochemical pharmacology. These include studies on development of methods for the measurement of hormones,

biogenic amines, and enzymes; the distribution and metabolism of hormones, the isolation and characterization of enzymes involved in hormone and biogenic amine metabolism. The laboratory examines control mechanisms of the biochemistry of the pineal gland and membranes.

• Section on Histopharmacology —Dr. David M. Jacobowitz

This section studies monoaminergic nerves (noradrenergic, dopaminergic, serotonergic) and cholinergic and gabaminergic neurons in the brain and the peripheral autonomic nervous system. A major aim of this section is to study the basis of behavioral regulation by a multidisciplinary approach to central neurotransmitter systems. Histochemical and neurochemical analyses are carried out at the level of discrete central nuclei and pathways in order to define the underlying bases for behavioral changes. Using the catecholamines histofluorescence method, the study of drugs, stress, and surgical stereotaxic lesions is used to correlate changes in neuronal function with various parameters of behavior. Behavioral studies being pursued involve the genetic fat rat, spontaneous hypertensive rat, sexual and reproductive function, and various stress manipulations. Neuronal amines, enzymes and peptides are measured within specific brain nuclei, tracts and other discrete regions of the brain using a microdissection method and radioisotopic assays. Immunofluorescence and radioimmunoassay are also being used to study the localization of enzymes (DβH) and peptides (α-MSH, bombesin, enkephalin, vasopressin, substance P) in the brain. Studies of peptides in human and animal brain and cerebrospinal fluid are currently underway. These are designed to examine the dynamics of release of peptides within the brain.

• Section on Medicine— Dr. Irwin J. Kopin

The research efforts of this group center around the study of biochemical and physiological effects of drugs and toxins which alter the formation, disposition, metabolism and receptor interaction of putative neurotransmitters and the enzymes which control their synthesis in both the central and peripheral sympathetic nervous systems. The techniques used include radioisotopic methods *in vivo* and *in vitro*, tissue slices, perfused organs, and organ and tissue cultures. Brain lesions, direct stimulation of specific areas in the brain, chronic indwelling catheters placed in arteries, veins, or cerebral ventricles, are used in studies in animals. Procedures are developed for application to clinical studies for evaluation of neurotransmitter and neuroendocrine function in human subjects. These studies are carried out in cooperation with other clinical units and include various disorders of the autonomic nervous system (orthostatic hypotension, hypertension, familial dysautonomia), neuropsychiatric disorders (Korsakoff's syndrome, Huntington's disease), as well as the major psychoses. Plasma, urine, and CSF are analyzed for various drugs, amines, and metabolites and the rates of utilization or synthesis determined using radioimmunological, enzymatic or mass spectroscopic techniques.

• Section on Experimental Therapeutics—Dr. Michael H. Ebert

The section conducts studies of the clinical pharmacology of a variety of neuropharmacological agents, including amphetamine and phencyclidine. Neurochemical, neuroendocrine, and pharmacokinetic experiments and drug trials are in progress in a variety of neuropsychiatric and psychosomatic syndromes. The section operates a clinical research unit to pursue these studies. In collaboration with other investigators in the Laboratory of Clinical Science, experiments are in progress in primates and man to measure turnover rates of brain monoamines by stable isotope labeling techniques, and changes in synthesis rates produced by disease

states and/or pharmacological treatment. Diseases of interest at the present time include orthostatic hypotension, anorexia nervosa, several presenile dementias, and hyperactivity in children.

• Unit on Pharmacological Applications of Mass Spectrometry—Dr. Sanford P. Markey

The unit develops techniques for clinical studies of neurotransmitters, neurohormones, peptides and their metabolites, and drugs which influence their formation or disposition. Projects include the synthesis of stable isotope-labeled analogues of amines and metabolites for human kinetic studies, the isolation and quantitative assay of compounds of interest, and the design and construction of alternate ion sources for mass spectrometry. Current projects include the synthesis of ^{18}O-dopamine as a probe of peripheral norepinephrine metabolism in humans, the negative ion mass spectral quantitation of levels of melatonin in plasma and its alteration by disease and pharmacologic intervention, and the assay of the major urinary melatonin metabolite for developmental studies in neonates, infants, and children.

• Unit on Neuroendocrinology—Dr. Michael J. Brownstein

The members of the unit are trying to locate peptidergic neurons in the central nervous system and to characterize them anatomically. In addition, investigations on how peptidergic neurons synthesize, transport, store, and release their biologically active products are in progress. The focus of these studies is to show how these processes are regulated by hormones and neurotransmitters.

Laboratory of Developmental Psychology—Dr. Marian R. Yarrow

Behavioral studies of children are in progress relating to the effects of stressful biomedical or psychosocial conditions on the functioning of children. Social, emotional, and intellectual competencies and disturbances are investigated. The biomedical conditions studied include juvenile diabetes, cancer, and malnutrition. Studies are also being conducted on the effects of parental and family pathology on child behavior. The rearing environments of these children and also the children's disabilities and coping skills are being investigated intensively. Among the risk groups being studied are children with a mentally ill parent. In all of this research, studies of normal child development and rearing are included.

Studies of the development of altruistic and aggressive behavior in children are also underway.

A standardized system is being developed for assessing patterns of problem behavior among children. It is being standardized for different age groups from 4 to 16 years and for each sex. It is being utilized in studies evaluating the effectiveness of different kinds of therapies for different kinds of behavior disturbances among children.

Division of Biological and Biochemical Research—Dr. John C. Eberhart

Laboratory of Neurobiology—Dr. Ichiji Tasaki

Current research projects include electrophysiological and biochemical studies of the mechanism of nerve excitation and conduction. Minute electric responses of the nerve membrane (less than about 5 microvolts in amplitude) evoked by various chemical stimulants have recently been discovered by a member of the laboratory and are being analyzed. Another electrophysiological project involves a detailed study of the basis of the bionic action potential in the perfused squid giant axon. Biochemical projects include the use of radioactively labeled neurotoxins such as saxitoxin to probe, isolate and study proteins involved in nerve conduction. In addition, membrane proteins from perfused squid giant axons are being studied by labeling them with various radioactive probes and analyzing

them using electrophoresis techniques.

Laboratory of General and Comparative Biochemistry—Dr. Giulio L. Cantoni

Investigations are concerned with the mechanisms and pathways of biological methylation, alkaloid biosynthesis, opioid peptides, cellular differentiation, and gene expression in eukaryotes. The main focus of the laboratory is on the enzymatic mechanisms in methyl transfer reactions, mechanism of drug addiction, muscle differentiation in cell culture, and genetic engineering.

- Section of Alkaloid Biosynthesis —Dr. S. Harvey Mudd

This section studies the enzymes involved in biosynthesis in methylation in plants and their control. The section also studies enzymatic mechanisms of transmethylation and intermediary metabolism of sulfur-containing amino acids in various conditions, including inborn errors of metabolism.

Laboratory of Cerebral Metabolism—Dr. Louis Sokoloff

- Section on Developmental Neurochemistry—Dr. Louis Sokoloff

A broad program of investigation is conducted on the biochemical aspects of growth, development, maturation, and regulation of metabolism in the CNS. These investigations are pursued at various levels, from molecular biology through enzymology and biochemistry, to whole animal physiology. Of particular interest are chemical compounds, such as hormones that play important physiologic roles in CNS function. A method recently developed in this laboratory permits the measurement of the rates of cerebral glucose consumption in the structural and functional components of the brain in conscious laboratory animals. This method is being applied in a variety of physiologic, pharmacologic, and pathologic states.

Laboratory of Neurochemistry —Dr. Seymour Kaufman

The following areas are studied: the structure, mode of regulation, and mechanism of action of phenylalanine hydroxylase, and the ancillary enzymes that comprise the phenylalanine-hydroxylating system. In addition to studies with the pure enzymes, emphasis is placed on the relationship between the properties of this enzyme system and the pathophysiology of phenylketonuria and hyperphenyalaninemia. This laboratory investigates the structure and regulatory properties of the enzymes involved in the biosynthesis of norepinephrine and serotonin, the relationship between the properties of the enzymes, and physiologic regulation of rates of synthesis of these neurotransmitters; the biochemical basis for skeletal muscle hypertrophy including the effects of exercise and neural factors in the process; cell-surface membrane proteins and receptors in their role in cellular differentiation; and the biochemical basis of genetic recombination, especially the integration of viral DNA into host chromosomes.

Laboratory of Neurophysiology —Dr. Edward V. Evarts

This laboratory conducts research on neural control of movements, plasticity of stimulus-response relations, and anatomic and histochemical correlates of brain activity.

The studies on neural control of movement are designed to elucidate the functional interrelations between motor subsystems (spinal cord, brain stem, cerebellum, basal ganglia, thalamus, and cerebral cortex). This work involves behavioral, electrophysiologic, and neuroanatomic techniques. Projects are aimed at understanding reflex and voluntary motor function. Studies on the control of eye movements focus on the vestibulo-ocular reflex and on saccadic movements. Discharges of single nerve cells are recorded with microelectrodes in monkeys trained to

Changes of neuronal activity are associated with anatomic and histochemical alterations. Studies are currently focused on the nature of these alterations in relation to circadian rhythms and motor activity.

Laboratory of Brain Evolution and Behavior—Dr. Paul D. MacLean

Opportunities are offered for research on evolutionary, developmental, ethologic, and ecologic factors relating to brain function and behavior. Large outdoor and indoor habitats are available for comparative studies on reptiles, birds, and mammals living under seminatural conditions. The laboratories are equipped for neuroanatomic research, microelectrode recording, brain stimulation, and psychological testing and have a computer system with high-speed graphics capability for the recording and processing of electrophysiologic and behavioral data. Research emphasis is on the role of primitive systems of the forebrain in genetically constituted, species-typical behavior; the influence of early experience on development; and the effects of crowding on social and individual behavior.

There is current work on reptilian embryology and fossil preparation. Weekly seminars are interdisciplinary in scope, dealing with subjects of interest to workers in neuroanatomy, neurophysiology, neurochemistry, ethology, psychology, ecology, paleobiology, and systematics. The laboratory is located at the NIH Animal Center near Poolesville, Maryland.

Division of Special Mental Health Research—Dr. Richard J. Wyatt

This division, located at St. Elizabeths Hospital, conducts a program of intramural research on special mental health problems such as psychopharmacology, neuropharmacology, neuroanatomy, memory, and human behavior. Clinical evaluations, treatment and followup are an integral part of all research protocols.

Laboratory of Clinical Psychopharmacology—Dr. Richard J. Wyatt

This clinical research laboratory capitalizes on many disciplines in its effort to understand and treat schizophrenia, the psychiatric problems of the elderly, and sleep disorders. The laboratory is set up so that small groups of young scientists may employ biochemistry, structural anatomy, pharmacology, physiology, and psychology in their work with these disorders.

- Unit on Clinical Studies—Dr. Llewellyn B. Bigelow

The major focus of the laboratory's research is directed by this Unit's exploration of innovative treatments. Three 12-bed research wards housed in a building devoted to schizophrenia research are the major resource. In addition, some of the 2,600 inpatients in Saint Elizabeths Hospital participate in research. New treatments are administered to examine their clinical effect and to help understand the basic mechanism of the schizophrenic disorders.

- Section on Psychophysiology of Schizophrenia—Dr. Thomas D. Reynolds

This section is committed, not only to psychophysiology, but to mathematical modeling of schizophrenia. Using frequent measurements of defined behaviors, mathematical models are formulated to describe changes in behavior, predict when they will occur in the future, measure the effects of experimental treatments, and understand the behavior's basic physiology.

- Group on Animal Behavior—Dr. David Stoff

Using a wide range of paradigms in a diverse group of animals, behaviors are monitored to understand basic processes and psychopathology. Issues such as tolerance to drugs, experimental diets, interactions of drugs with one another and with hormones are examined.

- Group on Mass Spectrometry—Dr. Farouk Karoum

The laboratory operates two quadrupole mass spectrometers which are primarily used in clinical studies to measure neurotransmitters and their metabolites. A major current interest is measuring phenylethylamine (PEA), an endogenous amphetamine-like compound, in schizophrenic patients.

- Group on High Pressure Liquid Chromatography—Dr. Leonard Neckers

This group has been instrumental in developing rapid, reliable, inexpensive assays for clinical investigations. Currently it is involved in measuring blood amino acids to determine if some schizophrenic patients are heterozygotic for phenylketonuria.

This group has also been responsible for developing an assay in the human lymphocyte for monoamine oxidase activity, using tissue culture techniques and immunology.

- Group on Enzymology—Drs. David Wise and Bruce Phelps

This group is principally interested in exploring the significance of the decreased monoamine oxidase which has been reported in some schizophrenic patients. Clinical materials are routinely assayed and physiochemical properties examined with the aim of understanding the significance of these deficits. The laboratory is currently purifying the monoamine oxidase from the human platelet and making antibodies to it.

- Group on Geriatric Psychiatry—Drs. Wallace Mendelson and William Freed

This group is examining the psychiatric problems of the geriatric population in collaboration with the National Institute on Aging and the National Institute of Neurological and Communicative Disorders and Stroke. Current studies include the evaluation of aluminum metabolism in Alzheimer's disease, metabolism of drugs in the aging, and examining the potential of brain grafting. The laboratory is also studying the behavioral effect of a number of peptides.

- Unit on Sleep Studies—Dr. J. Christian Gillin

The Unit on Sleep Studies is located both at Saint Elizabeths Hospital and the Clinical Center in Bethesda.

This unit studies the sleep patterns of patients on clinical units at the two NIMH facilities. Its primary goal is to elucidate basic physiological processes relating to sleep and dreams, as well as disorders of sleep. It is also involved in studies of human memory, including the development of pharmacological approaches which may affect learning and memory. The animal facility, located at Saint Elizabeths Hospital, utilizes pharmacological and electrophysiological techniques to study sleep.

Laboratory of Preclinical Pharmacology—Dr. Erminio Costa

Scientific efforts of this laboratory are directed toward the elucidation of neuronal control mechanisms that mediate responses of drugs affecting neuronal function. The laboratory is organized into one group and four sections.

- Group on High-Pressure Liquid Chromatography—Dr. James Meek

New methods are developed to investigate drug effects on renovation rates of brain stores of monoamines and neuropeptides.

- Section on Molecular Pharmacodynamics—Dr. Darwin Cheney

Pharmacologic studies are conducted on the dynamics of acetylcholine in discrete brain nuclei using pulses of deuterated precursors and mass fragmentography, the dynamics of GABA in discrete brain nuclei using pulse labeling with ^{13}C glucose and mass fragmentography, and the regulation of the dynamics of acetylcholine and GABA by various endogenous neuropeptides.

- Section on Biochemical Pharmacology—Dr. Norton Neff

This section conducts investigations directed at the identification of control mechanisms for enzymes that regulate the dynamics of putative

brain neurotransmitters and the determination of drug actions on the regulation of turnover rate of brain monoamines using mass fragmentography.

- Section on Neuroendocrinology —Dr. Alessandro Guidotti

Studies concern the molecular mechanisms involved in the transsynaptic induction of tyrosine hydroxylase and the activation of cAMP-dependent protein kinases in relation to the neuroendocrine control of pituitary and pineal glands.

- Section on Molecular Neurobiology—Dr. Erminio Costa

Investigations are conducted on the regulation of nerve growth factor production by glial cells; the role of chromatine phosphorylation in the regulation of gene expression; the pharmacology of binding of putative neurotransmitters to postsynaptic receptors; the regulation of storage, release, and synthesis of peptides that function as putative neurotransmitters (enkephalines, substance P, angiotensin, and neurotensin); and the identity and kinetic properties of enzymes that regulate the synthesis and metabolism of neuropeptides.

carry out movements, and the results are interpreted in relation to the anatomic input-output properties of the loci from which recordings are obtained.

Work in the area of plasticity of stimulus-response relations involves the role of segmental and suprasegmental neural factors in determining the modifications of muscular activity associated with motor learning in man and subhuman primates. Studies also focus on mechanisms underlying adaptive changes in the vestibulo-ocular reflex in the monkey.

National Institute of Neurological and Communicative Disorders and Stroke

Donald B. Tower, M.D., Ph.D., Director

Thomas N. Chase, M.D., Director, Intramural Program

Donald B. Calne, D.M., F.R.C.P., Clinical Director

Richard L. Irwin, Ph.D., Laboratory Director

Clinical Associates

Clinical associate positions for the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) are available in medical and surgical neurology, experimental therapeutics, infectious diseases, neuroimmunology, and developmental and metabolic neurology. Associates are appointed for 2 years, with the possibility of extended affiliation.

Major components of the Clinical Associate Program include patient care responsibilities on NINCDS wards, involvement in consultative services at the NIH Clinical Center, and participation in laboratory investigations.

Clinical associates have the opportunity to work closely with senior investigators, to attend onsite courses and conferences, and to pursue their own research interests within the context of ongoing clinical programs and current NINCDS research emphases.

Candidates requiring further information about NINCDS clinical associate positions should write to Dr. Thomas N. Chase, Director, Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, Bldg. 36, Room 5A05, NIH, Bethesda, Maryland 20205.

Research Associates

NINCDS research associateships are available in molecular biology, neurochemistry, neurophysiology, neuropathology, and other areas of fundamental neuroscience investigation. Appointments are for 2 years, with the possibility of extended affiliation.

Areas of study are developed by each associate in conjunction with a preceptor. In general, the resultant research program will relate to the ongoing mission and activities of the laboratory to which the associate is assigned. Independence and originality of approach are encouraged.

Research associates have the opportunity to work closely with a large and diverse group of senior investigators, to participate in onsite courses and conferences, and to employ advanced neuroscience technology in the conduct of their research.

For further information on the NINCDS Research Associate Program, write to Dr. Thomas N. Chase, Director, Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, Bldg. 36, Room 5A05, NIH, Bethesda, Maryland 20205.

Staff Associates in Epidemiology

Office of the Director—Thomas N. Chase, M.D., Director

- Section on Neuroepidemiology —Dr. Bruce S. Schoenberg and Dr. Roswell Eldridge

The Section conducts national and international studies concerning the patterns of neurologic disorders in human populations. Both environmental and genetic factors in disease etiology are considered. The associate receives training in the utilization of neuroepidemiologic and neurogenetic techniques to the solution of practical problems in clinical neurology and neurosurgery. Although the Section's program involves the application of epidemiologic methods to the study of any disorder of the nervous system, current research concentrates on cerebrovascular disease, brain tumors (including neurofibromatosis), dementia, cerebral palsy, torsion dystonias, multiple sclerosis, parkinsonism, and racial differentials in the occurrence of neurologic disease.

Clinical Branches

Clinical Neurosciences Branch—Dr. Susumu Sato

Various clinical and electroencephalographic (EEG) aspects of seizure disorders are investigated, with emphasis on localization. Cerebral evoked response techniques are also applied for clinical seizure research. EEG and cerebral evoked response examination is provided for patients referred from the entire Clinical Center. The appointment of clinical associates (with preference for persons with experience in clinical neurology) is for 2 years. Basic investigation is focused on pathophysiologic aspects and pharmacologic aspects utilizing a kindling model of epilepsy. Research associates are appointed for 2 years. Preference is given to persons with some experience in the fields of electrophysiology and/or electronics or neuroanatomy.

Developmental and Metabolic Neurology Branch—Dr. Roscoe O. Brady

- Section on Enzymology and Genetics—Dr. Roscoe O. Brady

Principal research efforts concern the pathologic biochemistry, diagnosis, carrier identification, and genetic counseling related to inherited disor-

ders of lipid metabolism such as Gaucher's disease, Niemann-Pick disease, Fabry's disease, Krabbe's disease, and Tay-Sachs disease, along with the development of enzyme purification procedures for replacement therapy trials. Other studies include alterations of complex lipid metabolism in neoplastic cells and the role of trophic hormones with cell membrane receptors.

- Section on Neurochemical Methodology—Dr. Andrew E. Gal

This section is involved in the preparation of widely useful substrates for the facile diagnosis of metabolic disorders, the development of ultramicroanalytic procedures for monitoring the effects of enzyme replacement therapy, and the synthesis of novel lipids and lipid analogues for metabolic studies in normal and pathologic tissues.

- Section on Myelin and Brain Development—Dr. Richard H. Quarles

Research is primarily concerned with the composition and metabolism of myelin components in the developing nervous system and an examination of abnormalities of their structure and function in demyelinating conditions such as multiple sclerosis.

- Section on Physiology and Metabolism—Dr. Eberhard G. Trams

Principal research involves the delineation of the molecular basis of nerve excitation as related to structural and functional sidedness of natural and artificial membranes.

- Section on Clinical Investigations and Therapeutics—Dr. John A. Barranger

Investigations are concerned with heritable and acquired disorders of metabolism, with emphasis on the elucidation of pathogenetic mechanisms and the development of measures for the treatment of these conditions including replacement of enzymes in deficiency disorders.

Experimental Therapeutics Branch—Dr. Donald B. Calne

- Section on Therapeutics—Dr. Donald B. Calne

The major effort of this section is directed at the development of drugs to improve the treatment of parkinsonism; in particular, agents that modify dopaminergic transmission are under investigation.

- Section on Pharmacology—Dr. Thomas N. Chase

This section is primarily concerned with the generation of new strategies for the pharmacotherapy of choreatic and dyskinetic disorders by the manipulation of neurotransmitter activity.

- Section on Clinical Epilepsy—Dr. Roger J. Porter

The major effort of this section is the intensive monitoring of patients with uncontrolled seizures by videotape recordings and telemetered electroencephalography, the study of the metabolism and efficacy of various antiepileptic agents, and studies on the usefulness of new scanning procedures, such as positron emission tomography.

- Unit of Biochemical Neuropharmacology—Dr. John Kebabian

Research is conducted on the biochemical properties of synaptic receptor mechanisms in the central nervous system (CNS) and drug-induced modification of receptor activity.

- Unit of Physiological Neuropharmacology—Dr. Judith Walters

Measurements are undertaken to evaluate the effects of drugs on the electrical discharges of single nerve cells in various regions of the CNS.

Infectious Diseases Branch—Dr. John Sever

- Section on Immunochemistry and Clinical Investigations—Dr. Sidney Houff

The pathogenesis of multiple sclerosis, amyotrophic lateral sclerosis, and progressive multifocal leukoencephalopathy is under study. Persistent perinatal infections are also being investigated. The role of viruses and cellular immune responses in patients and experimental animals is being

tested. Clinical work is done on abnormal antibody and cellular immune reactions in these patients.

• Section on Neurovirology—Dr. Maneth Gravell

This section is involved in research on viruses as causes of tumors of the brain. Reye's syndrome, and cerebellar disease with infectious mononucleosis (Epstein-Barr virus), as well as experimental models of persistent virus infections. Methods include tissue culture, cocultivation, new tests for cellular immunity, and antibody determinations.

• Section on Experimental Pathology— Dr. W. T. London

Studies of perinatal infections that cause birth defects and persistent central nervous system infections are conducted in monkeys and small laboratory animals. Papovaviruses, cytomegaloviruses, toxoplasmosis, and herpesviruses are being used. Methods for direction, treatment, and prevention are being developed. Practical applications include vaccine development, rapid diagnostic tests, and assessment of new antimicrobial agents.

• Section on Electron Microscopy —Dr. Monique Dubois-Dalque

This section uses high-resolution scanning electron microscopy and immunoperoxidase labeling to study mechanisms of acute and chronic infection of disassociated infected nerve cells; interactions between antibodies, lymphocytes, and the surface of virus-infected cells; and the brains of animals and patients with acute and chronic viral infections and/or demyelinating diseases.

One clinical associate is appointed annually for 2 years. This individual participates in clinical research and may become involved in one of the above areas. Persons with Ph.D. or M.D. degrees with equivalent research experience are appointed as research associates for a 2- or 3-year period. These individuals perform basic research relevant to neurologic disease.

Medical Neurology Branch—Dr. John Sever

• Section on Neuromuscular Diseases—Dr. W. King Engel

As its major function, this branch is involved in the application of basic techniques to the investigation of clinical neurologic problems. The clinical associate becomes intimately acquainted with many of the neurologic diseases, with particular emphasis on neuromuscular diseases that encompass disorders of muscle, myasthenia gravis, peripheral neuropathies, and lower motor neuron disease, as well as certain other metabolic and genetically determined CNS disorders. The associate receives instruction in clinical neurology and the related clinical and basic sciences while developing an understanding of the various laboratory techniques that support the detailed clinical-scientific neurologic investigation. During the first 12 months the clinical associate is in a research ward environment and is responsible for the care of patients on the Medical Neurology Service and the integration of related research. The associate covers the neurologic consultations to the other clinical services during 3 of those months. During the first year, the clinical associate also learns to perform one of a variety of basic laboratory techniques (such as in histochemistry, biochemistry, electron microscopy, immunology, autoradiography, tissue culture, or electromyography) as it applies to a clinical problem. The second year is spent in full-time work on that clinical research technique. Some clinical associates may stay a third year to continue their clinical research activities. A clinical associate may elect to come for 1 year only, but 2 years is preferable. The 2-year program is accredited for 1 year of residency training in neurology.

Surgical Neurology Branch—Dr. Paul L. Kornblith

This branch investigates and treats clinical problems of disordered neuronal and glial proliferation and

differentiation. A major part of the program is devoted to the study of intracranial tumors including pituitary tumors. Problems of both central and peripheral neuronal and glial regeneration are also under study. Clinical research in these areas is combined with basic techniques of cell biology, tissue culture, biochemistry, immunology, pharmacology and light and electron microscopic histology to provide for an in-depth exploration and, ultimately, new approaches to these problems.

The mechanism of pain sensation is currently investigated in the neurophysiology laboratory. The responses of the nerve cells at different levels in the CNS are recorded in animals with extracellular or intracellular microelectrodes and pharmacological agents are applied through micropipettes.

Experimental neuropathology and neuroimmunology is emphasized in a program which includes clinical diagnostic neuropathology. Biochemistry, morphology, and immunochemistry of neoplasms are studied as means of improving detection and treatment and as clonal models of their nonneoplastic counterparts in nervous and lymphoid tissues.

Studies are being carried out on cell-mediated immune mechanisms in human brain tumor patients, including delineation of the effectiveness of various forms of cell-mediated immunity to contribute to the destruction of brain tumors, examination of the ability of brain tumors to elicit cellular immune responses both *in vivo* and in model systems *in vitro*, and exploration of possible modes of altering brain tumor cells so as to increase their immunogenicity. This work is complemented by studies in animal models on basic mechanisms of cell-mediated immune lysis of tumor cells.

The clinical associate participates in the care of patients on the various protocols of the Surgical Neurology Branch as well as consultative care of patients with neurosurgical problems in all the NIH Institutes. The associate receives training in the diagnostic and operative techniques of surgical neurology with special emphasis on microneurosurgery both in the animal laboratory and in the operating room. In addition, there will be opportunity for work in the laboratory with training in a wide range of cell biology techniques, with special emphasis on tissue culture, immunoneurology, and electron microscopy. Experimental surgery and other therapy in animal models as it relates to the clinical problems under study will also be performed. The clinical associate also works in collaboration with senior scientists or independently in specific laboratory areas as his or her experience and interest dictates.

- Section on Neuroradiology and Computed Tomography—Dr. Giovanni Di Chiro

Work in this section currently focuses on the latest applications of transmission computed tomography and its further development as a noninvasive method for morphologic and functional studies of the nervous system. The section is also very actively involved in emission computed tomography using positron emitting radionuclides (positron emission tomography). Particular emphasis is placed on correlative studies between transmission and emission computed tomography.

Neuroimmunology Branch—Dr. Dale E. McFarlin

Research is performed in the following areas: characterization of the immune response to viral agents, such as measles which cause chronic infection in patients with neurologic diseases; study of certain animal models; study of model autoimmune diseases such as experimental allergic encephalomyelitis; assessment of the immune response to components of membranes in the peripheral nervous system and CNS; evaluation of immune function in patients with chronic neurologic disorders of un-

known etiology, such as multiple sclerosis, and parkinsonism, which may be related to either a persistent infection of the nervous system or immunopathologic mechanisms; assessment of the immune reactivity in human diseases believed to have an autoimmune etiology such as myasthenia gravis; and assessment of new therapeutic agents which alter the immune response.

One clinical associate is appointed annually for 2 years. This individual participates in clinical research and may become involved in one of the above areas. Persons with Ph.D. or M.D. degrees with equivalent research experience are appointed as research associates for a 2- or 3-year period. These individuals perform basic research relevant to neurologic disease.

Basic Research Laboratories

Laboratory of Central Nervous System Studies—Dr. D. Carleton Gajdusek

This laboratory is engaged in two studies: 1) the complete medical surveillance of disease patterns in many primitive and isolated populations, with attention to child growth and development, behavior, and learning, and to the dynamics and population genetics of human evolution in such groups; and 2) the slow, latent, and temperate virus infections, with particular attention to chronic degenerative neurologic disease and basic virologic and immunologic studies on the pathogenesis of slow infections and on the mechanisms of virus persistence. Much of the program is centered on the atypical infections caused by conventional viruses of the subacute spongiform virus encephalopathy group (kuru, Creutzfeldt-Jakob disease, scrapie, and mink encephalopathy) that form a new group of microorganisms tentatively called "viruses," although they contain much smaller genetic information and possess very different properties than any other group of viral agents. The biologic and molecular characterization of these unconventional viruses is the major focus of the work. Aging of the brain, Alzheimer's, Parkinson's and Huntington's diseases, multiple sclerosis and amyotrophic lateral sclerosis and other diseases are intensively studied in laboratories and in foci of high incidence throughout the world. Aspects of learning and socialization in primitive disappearing cultures are documented with the use of still and sound cinema photographic recording and sound recording. New methods of handling such data are developed.

Laboratory of Neural Control—Dr. Robert E. Burke

Fundamental research is conducted on the properties of mammalian nerve cells and on the organization of the mammalian CNS with particular reference to studies of the control of movement. Current experimental studies involved three main areas: 1) the CNS control of spinal cord motoneurons and in turn the control exerted by these cells on the muscle fibers innervated by them; 2) the organization of information-processing systems in the spinal cord; and 3) the activity of motor cortex neurons and of individual peripheral afferents during normal movement in intact animals. Such studies utilize established as well as newly developed techniques for electrophysiologic recording from single neurons, but other methods, such as those of neuroanatomy or of muscle fiber histochemistry, are also used as appropriate. The laboratory has facilities for the development of specialized experimental equipment and novel electrode designs suitable for chronic implantation, as well as for computer-oriented data analysis and model building. The staff includes members with experience in neurophysiology, electronics, biomedical engineering, mathematics, and computer technology.

Laboratory of Neurochemistry—Dr. Janet V. Passonneau

Research is conducted on molecular events that underlie the normal functioning of the nervous system and derangements that occur in neurologic diseases.

- Section on Cellular Neurochemistry—Dr. Janet V. Passonneau

The section is involved in the study of the metabolism of the brain in gross and micro regions with the use of special micromethodology enabling one to measure 10^{-18} moles of metabolites and 10^{-15} moles of cyclic nucleotides. Studies include the effects of ischemia, anoxia, and experimentally induces seizures on *in vivo* and *in vitro* systems.

- Section on Enzyme Chemistry—Dr. Wayne Albers

The enzymatic mechanism of active Na^+ and K^+ transport is investigated. Other current projects involve γ-aminobutyric acid metabolism, brain mitochondria, and membrane receptors.

- Section on Neuronal Development and Regeneration—Dr. Andrew Zalewski

This section is attempting to elucidate the factors involved in nerve fiber regeneration, trophic nerve function, and selectivity and plasticity in the formation of neural connections. A variety of neurohistologic, histochemical transplantation, and immunologic techniques are being used in these studies.

Laboratory of Neuro-Otolaryngology—Dr. Jorgen Fex

Inner ear neuronal mechanisms are being studied in mammals. The long-range purpose of the project is to study the biochemistry, morphology, pharmacology, and physiology of inner ear neurons and cells and their interactions and to describe the mechanisms of these interactions. A second project concerns the synaptic transmission and neuronal connections of the mammalian cochlear nucleus. A multidisciplinary approach is being used for this project. A major, long-term program of this laboratory is to solve problems concerning hereditary deafness in man; mutants of mice and guinea pigs with genetic inner ear deficiencies will be used as models.

Laboratory of Neuropathology and Neuroanatomical Sciences—Dr. Igor Klatzo

- Section on Functional Neuroanatomy—Dr. Thomas Reese
- Section on Neurocytology—Dr. Milton Brightman
- Section on Experimental Neuropathology—Dr. Jan Cammermeyer
- Section on Cerebrovascular Pathology—Dr. Igor Klatzo
- Section on Cellular Neuropathology—Dr. Henry Webster
- Section on Neurocytobiology—Dr. Maria Spatz

The laboratory recognizes the scientific advantages to be derived from close contact in the interaction between various approaches used in the fields of neuropathology and neuroanatomic sciences. Thus, investigations on mechanisms operative in various neuropathologic conditions are carried out in parallel with or supported by studies elucidating structural and functional features of the normal nervous system. Specific problems under current investigation are cerebral ischemia, hypoxia, brain edema, physiology of the blood-brain barrier, development and pathology of myelin, aspects of vascular permeability and transport mechanisms in the brain, neural membranes, elucidation of junctional complexes, and the source and fate of synaptic vesicles, as well as some of the sensory and motor systems. The main technical approaches include light and electron microscopy; freeze-fracturing; scanning microscopy; histochemistry; radioisotopic, biochemical, and microchemical assays; and tissue culture.

Laboratory of Neurophysiology—Dr. H. G. Wagner

Research is conducted on the basic properties of nerve cells and on the nervous system. Central neurons and peripheral receptors are studied by bi-

ophysical and chemical means with respect to their membrane properties; transduction of external effector stimulus into neural processes; and the selection, generation, and transfer of information through and between neurons.

- Section on Sensory Physiology —Drs. T. G. Smith and J. L. Barker

This section investigates the biophysical and pharmacologic properties of membranes and synapses in simple neural systems including tissue-cultured neurons.

- Section on Cell Biology—Dr. A. Lasansky

Investigations focus on electrophysiologic function correlated with the microscopic and ultramicroscopic study of morphologic structure in the neural pathways of the vertebrate retina.

- Section on Neuronal Interactions —Dr. H. G. Wagner

Attention is on the selection, coding, and transfer of information through and between neurons of the visual system.

Laboratory of Molecular Biology —Dr. Ernst Freese

The molecular mechanisms of the developmental and lethal effects of mutations, viruses, and drugs on cells in culture are examined. These mechanisms are correlated to hereditary or viral diseases and to teratogenic effects.

- Molecular Virology Section—Dr. R. A. Lazzarini

The control of cellular and viral RNA synthesis is studied in tissue cultures. In particular, the transcription and replication of the myxoviruses and paramyxoviruses are examined at the molecular level.

- Section on Developmental Biology —Dr. Ernst Freese

The control of cell differentiation is studied in bacteria, yeast and mammalian cells by the use of mutations and drugs. The observed effects are examined in terms of metabolism, and the control of nucleic acid, enzyme, wall and membrane synthesis. The molecular mechanisms are analyzed by nucleic acid hybridization, as well as enzyme, membrane, and receptor properties. In addition, mouse embryo cultures are used to measure the development of drug sensitivity and the response to potential teratogens.

Neurological Disorders Program Dr. F. J. Brinley, Jr.

The goal of the Neurological Disorders Program is to plan and direct a program of grant and contract support for research and research training on neurologic disorders to insure maximum utilization of available resources for the attainment of Institute objectives and to collaborate with intramural programs within the Institute and NIH-wide. The program is charged with the study of national priority diseases such as epilepsy; neurologic disorders of the aging; developmental disorders of children and adults; sclerosing and neuromuscular disorders; infectious diseases of the central nervous system; neuroendocrine studies; and learning, behavior, and other sensory disorders. A number of the studies underway are conducted in collaboration with outside institutions. The following programs are conducted by the Neurological Disorders Program of the NINCDS.

Epilepsy Branch—Dr. Roger J. Porter

This branch develops and coordinates organized and directed research programs on a multi-institutional, geographic, or multidisciplinary basis through its support of five comprehensive programs, each serving a specific geographic area. It develops, conducts, and coordinates collaborative and directed research programs aimed at finding new or improved methods of diagnosis, treatment, and prevention of convulsive disorders. The clinical investigation of new antiepileptic drugs is a major concern. The branch fosters the synthesis, screening, and pharmacologic and metabolic investigation of antiepilep-

tic drugs by collaborative efforts; conducts research on the metabolism of anticonvulsant drugs and the treatment of certain difficult seizure disorders according to rigid protocols within its own facilities; fosters research in experimental models of epilepsy and improved patient treatment through the use of serum antiepileptic drug determinations.

Developmental Neurology Branch
—Dr. Joseph S. Drage

The branch plans and implements a program of grant- and contract-supported research on the neurologic basis of developmental disorders of children, including the areas of cerebral palsy, autism, mental retardation, learning and behavioral disorders, central nervous system birth defects, heritable muscle and neurologic diseases, and minimal brain dysfunction; assesses the need for research and research training in such areas; determines and recommends program priorities and funding levels for such areas; consults with professional and voluntary health organizations in identifying, developing, and implementing a research program focused on the neurologic basis of development disorders of children; provides for the archival and retrieval system of the Collaborative Perinatal Project data, and promotes the appropriate use of this national data resource commensurate with the goals and mission of the NINCDS.

The Clinical Center

Mortimer B. Lipsett, M.D.,
Director

Griff T. Ross, M.D., Ph.D.,
Deputy Director

Blood Bank Department—
Dr. Paul V. Holland

Staff Fellowship

The Blood Bank Department accepts applications for an American Medical Association accredited fellowship program in blood banking and immunohematology. The fellowship assignment can be for 1 or 2 years. Vacancies do not necessarily occur each year. Board certification or eligibility in internal medicine, clinical pathology, or hematology is desirable.

The program offers training in the management of a patient-oriented transfusion program as well as specialized training for the hematologist and clinical pathologist. The fellow receives broad experience in all aspects of blood banking, including clinical and laboratory immunohematology, pheresis techniques, donor recruitment, and blood component preparation and therapy. The associate participates actively in the service and teaching functions of the Blood Bank.

Involvement in a clinical or basic research project is encouraged. As a focal point in patient care and as a repository of diverse blood samples, the Blood Bank provides a unique opportunity for collaborative research with the various Institutes. Current programs include investigations into the various agents responsible for post-transfusion hepatitis, the effects of biologic incompatibilities on transfusion and transplantation, and immunologic studies of drug-induced hemolytic anemias.

Prospective applicants desiring more information should write to Paul V. Holland, M.D., Chief, Blood Bank Department, Building 10A, Room 1E33, NIH, Bethesda, Maryland 20205

Clinical Pathology Department—

Dr. Ronald Elin

Clinical and Research Associates

The Clinical Pathology Department offers a broad spectrum of laboratory diagnostic services for intramural patient care for the Institutes. The department is organized into four services: clinical chemistry, hematology, microbiology, and laboratory computer service. The Clinical Chemistry, Hematology, and Laboratory Computer services offer associate positions, but not necessarily on a yearly basis.

- Clinical Chemistry

The Clinical Chemistry Service provides all the chemical diagnostic tests on the patients in the Clinical Center, as well as for outpatient clinics. The senior staff is composed of seven individuals with M.D. and/or Ph.D. degrees. Approximately 100,000 tests are performed per month by a technical staff of 42 medical technologists, chemists, technicians, and medical aides. The Clinical Chemistry Service collaborates in clinical research of a chemical nature and conducts extensive research and development in analytic methodology, automation, and computerization. Current interests within the service are the development of radioimmunoassays, adaptation of the calorimeter for laboratory testing, electrophoresis, factors affecting the reference range, instrument evaluation, and automated assay.

A clinical or research associate entering this 2-year program would receive in-depth training in the various aspects of clinical chemistry. The first year of the program would be devoted to a rotation through the clinical chemistry sections—STAT tests, electrophoresis, radioimmunoassay, urinalysis, special chemistry and microchemistry. In addition, emphasis would be placed on the correlation of laboratory data with the status of patients. The associate would be encouraged to attend working patient rounds and to handle inquiries to the Clinical Chemistry Service from patient-care physicians. Also, during this first year, the associate would have the opportunity to develop specific interests in investigative studies. During the second year of the program, the associate would be encouraged to choose a research project for independent investigation under the supervision of a senior staff member or to participate in an ongoing research project.

Any candidate interested in the Clinical or Research Associate Programs should write to Ronald J. Elin, M.D., Ph.D., Chief, Chemistry Service, Clinical Pathology Department, Building 10, Room 5N-220, NIH, Bethesda, Maryland 20205.

- Hematology

The Hematology Service provides a combined laboratory-clinical experience in hematology. The service is responsible for the operation of the clinical and special hematology laboratories for patient care and has an active clinical service based on the patients with hematologic problems in the Clinical Center. In addition, the Hematology Service has an active program directed at clinical and developmental research in hematology. Research of particular interest concerns coagulation and platelet disorders, advances in morphologic interpretation of bone marrow material, purification and characterization of coagulation proteins, studies on platelet physiology and pathology, and the study of the role of carbohydrates on coagulation and platelet function. Other research endeavors include the use of markers for hematopathologic diagnoses and the development and testing of new procedures of analytic systems in the hematology laboratory.

The Hematology Service recruits clinical associates or research associ-

ates for a minimum of 2 years. Each clinical associate will spend at least 1 year doing primarily clinical work with patients in the Clinical Center. During this time, the associate will have the opportunity to develop specific interest in investigative studies. Associates will be encouraged to choose their own problem for independent investigation or to pursue, with the guidance and supervision available in the Hematology Service, a joint project with an established investigator. Research associates are assigned to highly qualified physicians to provide an opportunity to improve their backgrounds for careers in basic medical research. During their tenure, research associates will devote most of their time to laboratory research. The candidate who is chosen would be given an opportunity to choose an area of investigation, and a senior staff member would serve as his preceptor.

Any candidate interested in either program should write to Harvey R. Gralnick, M.D., Chief, Hematology Service, Clinical Pathology Department, Building 10, Room 5N236, NIH, Bethesda, Maryland 20205.

- Microbiology

The Microbiology Service provides in-depth training in various aspects of clinical diagnostic microbiology, as well as the opportunity to participate in ongoing developmental research projects. Although the training program is primarily laboratory based, opportunity is considerable for interaction with the Infectious Disease Service and other patient-care physicians. The Microbiology Service is responsible for the isolation and identification of bacterial, mycobacterial, mycologic, and parasitic pathogens in Clinical Center patients. Determinations of antibiotic sensitivity and antibiotic levels are also performed, as well as a variety of clinical serologic procedures. No viral, chlamydial, or rickettsial work is currently performed in our laboratory. Present research activities include the use of computers for the organization and utilization of microbiology laboratory data, the development and assessment of a lysis-filtration and impedance system for blood culturing, the use of laser light-scattering techniques for the determination of antibiotic synergy, the evaluation of new methodologies for antibiotic sensitivity testing, and the study of the ecology of a resistant *Coryne-bacterium* species. A variety of clinicopathologic studies are also undertaken or could be initiated under senior staff supervision.

Persons interested in a clinical or research associate position with the Microbiology Service should contact James D. MacLowry, M.D., Chief, Microbiology Service, Clinical Pathology Department, Building 10, Room 4D07, NIH, Bethesda, Maryland 20205.

- Laboratory Computer

The Laboratory Computer Service provides computer and statistical support for the patient-care and research programs of the Clinical Pathology Department. The service also conducts research on medical laboratory automation, computer-assisted interpretation of clinical laboratory measurements, variation in test results, and methods of quality control. The staff includes two pathologists as well as programmers, and computer operators. In addition to its own minicomputer systems, the service makes extensive use of the NIH IBM 370 and DEC PDP-10 time-sharing computers. Investigators in the service utilize extensive machine-readable files of clinical and laboratory information pertaining to NIH patients.

An associate works with the senior staff in applying computer and statistical techniques to problems of laboratory methods. Associates are encouraged to develop independent or collaborative research projects. In addition, they may participate in teaching conferences of the Clinical Pathology Department.

Interested candidates should write to Thomas L. Lewis, M.D., Chief, Laboratory Computer Service, Clinical Pathology Department, Building 10, Room 7D45, NIH, Bethesda, Maryland 20205.

Diagnostic Radiology Department—
Dr. John L. Doppman

Staff Associates

Staff radiologists are selected each year from among those applicants who have completed their residencies in diagnostic roentgenology (Board certification not required). Such appointments are made for a period of 2 years, with opportunity for reappointment.

The department is well equipped to provide the routine and special diagnostic radiographic examinations needed by the 50-55,000 patients seen each year. Ultrasound and computed tomography play an increasingly important role in the diagnostic and research activities in the department.

The preselection of patients for admission to NIH insures a challenging and stimulating gamut of diagnostic problems.

Thirteen radiologists comprise the professional staff, and an adequate supporting staff is provided.

Facilities are available for collaborative clinical and independent radiographic research projects. The development of new and more effective diagnostic techniques is encouraged and has proven possible in this program.

Close clinicopathologic correlations are made possible by frequent consultation and effective liaison with members of other department staffs.

Nuclear Medicine Department—
Dr. Gerald S. Johnston

Clinical Associates

One clinical associate is accepted each year for a 2-year period of investigative clinical research. Preference will be given to applicants with prior training in nuclear medicine. The specific field of previous residency training is not a primary consideration, but 1 year in approved internal medicine, radiology, or clinical pathology is recommended to meet the requirements for certification by the American Board of Nuclear Medicine.

Residency Training

The American Medical Association has approved the department for a 2-year residency training program in nuclear medicine. Qualifications for trainees include at least 2 years of prior training in radiology, pathology, or internal medicine. Residents will attend a 2-month basic course and spend 3 months each at Georgetown University Hospital or the Maryland University Hospital.

The department consists of four sections: the Diagnostic Nuclear Medicine Section, the Applied Physics Section, the Whole-Body Counter Section, and the Radiopharmacy Section.

The Diagnostic Nuclear Medicine Section provides clinical and investigative service to the physicians of the various Institutes working within the Clinical Center. Rectilinear scanners, gamma cameras, ultrasound, and a computerized tomography X-ray head unit are the basic imaging devices. Computers for processing nuclear medicine data are located within the section. Computer experts from the Division of Computer Research and Technology (DCRT) provide professional support for the development of computer-assisted nuclear medicine procedures. The Applied Physics Section and DCRT personnel work cooperatively in the development of new

diagnostic techniques. The Whole-Body Counter Section works closely with the Diagnostic Nuclear Medicine Section and the Radiation Safety Office. It operates three whole-body counters and provides a consultation service to all the Institutes. It is engaged in basic research on trace quantities of radioactivity, personnel monitoring, and a variety of clinical studies. The staffs of the Diagnostic Nuclear Medicine and Whole-Body Counter Sections consist of seven physicians, a radiobiologist, two physicists, an equipment specialist, eight nuclear medical technicians, and three clerks. Departmental professionals are encouraged to interact with members of the various Institutes to develop new diagnostic applications of radionuclides in the investigation of a variety of diseases. The Radiopharmacy Section employs three full-time radiopharmacists, a chemist, a technician, and a clerk to maintain quality control over radiopharmaceuticals used in humans as well as to compound many of the agents used by the Diagnostic Nuclear Medicine Section. This section also provides consultations and support for the use of radionuclides in diagnosis and research.

Division of Computer Research and Technology

Arnold W. Pratt, M.D.
Director

Research Associates

The Laboratory of Applied Studies, DCRT, offers 2 to 3-year research associate positions to highly qualified physicians with backgrounds in physical science or engineering (including mathematics through differential equations), two years' experience in computer programming, and at least one year's clinical experience beyond the M.D. degree.

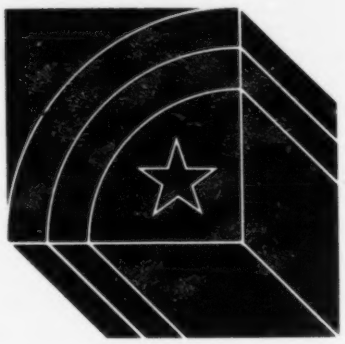
Laboratory of Applied Studies—Dr. Eugene K. Harris

This laboratory includes mathematicians, physicians, electronics engineers, statisticians and computer systems analysts engaged in collaborative studies with other biomedical scientists on modelling of physiological processes, especially transport, reaction-diffusion and receptor binding kinetics, and with clinicians on applications of image-processing and statistical analysis to the diagnosis of disease and assessment of treatment, particularly in pulmonary and cardiovascular-renal problems.

The Division in which this laboratory is located supports the world's most powerful, user-oriented biomedical computing facility. Working on one or more specific projects under the preceptorship of a senior investigator, the associate will have ready access to and gain familiarity with advanced interactive display devices, graphics terminals and programming systems for both clinical and basic research.

Part Four

Academic Programs Available to Associates



Among the academic programs open to an NIH associate are: evening courses provided by the Foundation for Advanced Education in the Sciences, Inc. (FAES); formal seminars under the direction of NIH staff; combined clinical staff conferences; formal lectures; and symposia. The "NIH Calendar of Events" lists 25 to 30 programs each week. Other events of interest are held at universities and institutions in the Washington-Baltimore area.

Evening Courses

Evening courses are provided by the Graduate Program of the FAES, established by scientists who subscribe to the view that learning, research, and teaching are mutually reinforcing processes essential to the evolution of science. The foundation is an independent organization whose tuition and fees can be paid by a Federal employer. The FAES also operates the NIH bookstore, which supplies textbooks and other reading material for the convenience of NIH staff.

Courses are offered in two semesters fall and spring. They are offered at the undergraduate and graduate levels under the programs of several departments of instruction: behavioral and social sciences, biochemistry, chemistry, genetics, mathematics, statistics, physics, medicine and physiology, microbiology and immunology, languages, and general studies. The FAES and the Clinical Center sponsor Board review courses in medicine and pediatrics. Subspecialty courses are offered for Board review in endocrinology, hematology, and oncology. Further inquiries regarding the Graduate Program and requests for its current catalog should be directed to: Registrar, The Graduate Program, Foundation for Advanced Education in the Sciences, Inc., National Institutes of Health, Bethesda, Maryland 20205.

Seminars

An NIH program of formal tutorial seminars and informal discussion groups is designed in content and emphasis for prospective independent investigators, and gives them the additional opportunity to master selected topics not adequately covered during college or graduate schooling. These seminars are now administered by the FAES, in conjunction with the evening courses. The program accommodates research, staff, and clinical associates and other properly qualified persons.

A number of tutorial seminars are generally made available each aca-

demic year in each of the following categories: biochemistry and genetics, cell biology, immunology, and physiology.

Weekly seminars run from September through January and from February through June. Each session is of 2 to 3 hours' duration, and the participants present specific material under the direction of an expert in the field. In preparation for these, the associate does appropriate outside reading.

Combined Clinical Staff Conferences and Lectureships

Aside from the rounds and staff conferences within the separate Institutes engaged in clinical research, the Clinical Center sponsors at least one monthly combined clinical staff conference for 8 months of the year. Each conference is conducted by one of the Institute services or an appropriate department of the Clinical Center. The conferences—open to the entire clinical staff and those engaged in laboratory research as well—center around clinical case material having interest for a large portion of the staff, and serve to keep individual investigators abreast of current emphasis in all clinical research.

Topics presented in the 1979-80 series were:

September 20, 1979	Dr. Ronald Crystal	Lung Disease
October 19, 1979	Dr. Reubin Andres	Aging
November 8, 1979	Dr. Alan Schecter	Sickle Cell Anemia
February 21, 1980	Dr. Stephen Katz	Herpetiformis Dermatitis
March 13, 1980	Dr. Michael Kaliner	Allergy, Asthma, and Cystic Fibrosis
April 24, 1980	Dr. Costan Berard	Malignant Lymphomas
May 15, 1980	Dr. W. King Engel	Neuropathies
June 5, 1980	Dr. Bruce Weintraub	TSH Secretion

Several formal lectures are presented annually. **The National Institutes of Health Lecture Series** was established in 1953 to recognize outstanding scientific accomplishment and to contribute to the interchange of scientific information. The lectureships are awarded by the Director of NIH on the advice of the scientific directors of the Institutes. The **R. E. Dyer Lectureship** was established in 1950 by friends and colleagues of Dr. Rolla E. Dyer, Director of the National Institutes of Health, 1942-50, to pay him tribute upon the occasion of his retirement from the Public Health Service. The award is made at appropriate times—usually on an annual basis—to a scientist who has made an outstanding contribution to knowledge in a field of medical science. Dr. Elvin A. Kabat presented a recent Dyer lecture on "Structural and Genetic Approaches to the Study of Antibody Complementarity." Among other distinguished speakers have been two Nobelists, Dr. Howard M. Temin, who spoke on "The Replication and Possible Origin of RNA Viruses with a DNA Polymerase" and Dr. D. Carleton Gajdusek, who discussed his work on "Kuru."

The **G. Burroughs Mider Lectureship** was established in 1968 by the scientific directors to honor Dr. Mider for his distinguished service to NIH. On advice of the scientific directors, these lectureships are awarded annually by the Director, NIH, to a scientist who has contributed significantly to the biomedical research eminence of NIH.

Recent Mider Lectures:

1980	Dr. Thomas Waldmann	The Control of the Immune Response Regulatory Cellular Interactions and the Control of Lymphocyte Differentiation
1979	Dr. Martha Vaughan	Regulation of Cyclic Nucleotide Metabolism
1978	Dr. Jesse Roth	Receptor Disorders in Man
1977	Dr. Philip Leder	A Close and Surprising Look at the Mammalian Genome
1977	Dr. Maxine F. Singer	Monkey Business: Sequences in the Monkey Genome and Their Interaction with Simian Virus 40 DNA
1975	Dr. Karl A. Piez	Collagen: Its Chemistry, Structure and Function
1974	Dr. Elizabeth F. Neufeld	Inherited Lysosomal Disorders Studied in Cell Culture
1973	Dr. Ira H. Pasten	Cyclic AMP and the Transformation of Cells
1973	Dr. Wallace P. Rowe	Genetic Factors in the Transmission and Expression of Murine Leukemia Virus

The Washington-Baltimore Educational Complex

The Washington-Baltimore area is widely known for its educational advantages. For example, three medical schools (Howard, Georgetown, and George Washington) are located in the District of Columbia and two (Johns Hopkins and the University of Maryland) are in Baltimore. These, and the universities with which they are associated, together with unique institutions such as the Armed Forces Institute of Pathology and the new Uniformed Services University of the Health Services at the National Naval Medical Center, offer exceptional opportunities. Some associates find the time to pursue a certain amount of formal education at such nearby institutions.

Library Facilities

The National Institutes of Health Library (located on the first floor of the Clinical Center) is an open stack, self-service library with a collection of some 230,000 volumes of medical and scientific books, and journals. Some 5,000 books and 3,800 journal subscriptions are received annually. Organizationally under the Division of Research Services, the NIH Library is an integral part of the research needs of the NIH staff. Its major subject areas include medicine, health sciences, chemistry, physiology, biology, physics and the peripheral areas of economics, education, legislation and social sciences. A full range of services is provided NIH employees, including library copy service, manual and on-line bibliographic service, interlibrary loan, advisory consultation for literature needs and a translating service.

The National Library of Medicine (NLM) is located on the NIH campus. While this library serves the en-

tire country, its proximity makes it specially valuable to NIH investigators. Holdings exceed 2 million items—books, journals, theses, pamphlets, prints, and microfilm. Researchers may consult material at the library and may request printed material through the NIH interlibrary loan service. Access to the library's computerized data base of journal references (MEDLINE) is available both at NLM and at the NIH library.

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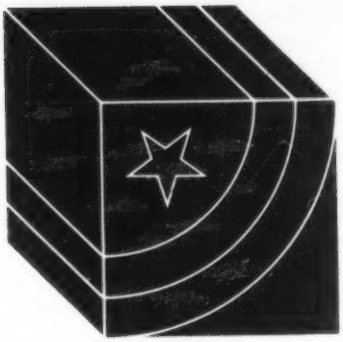

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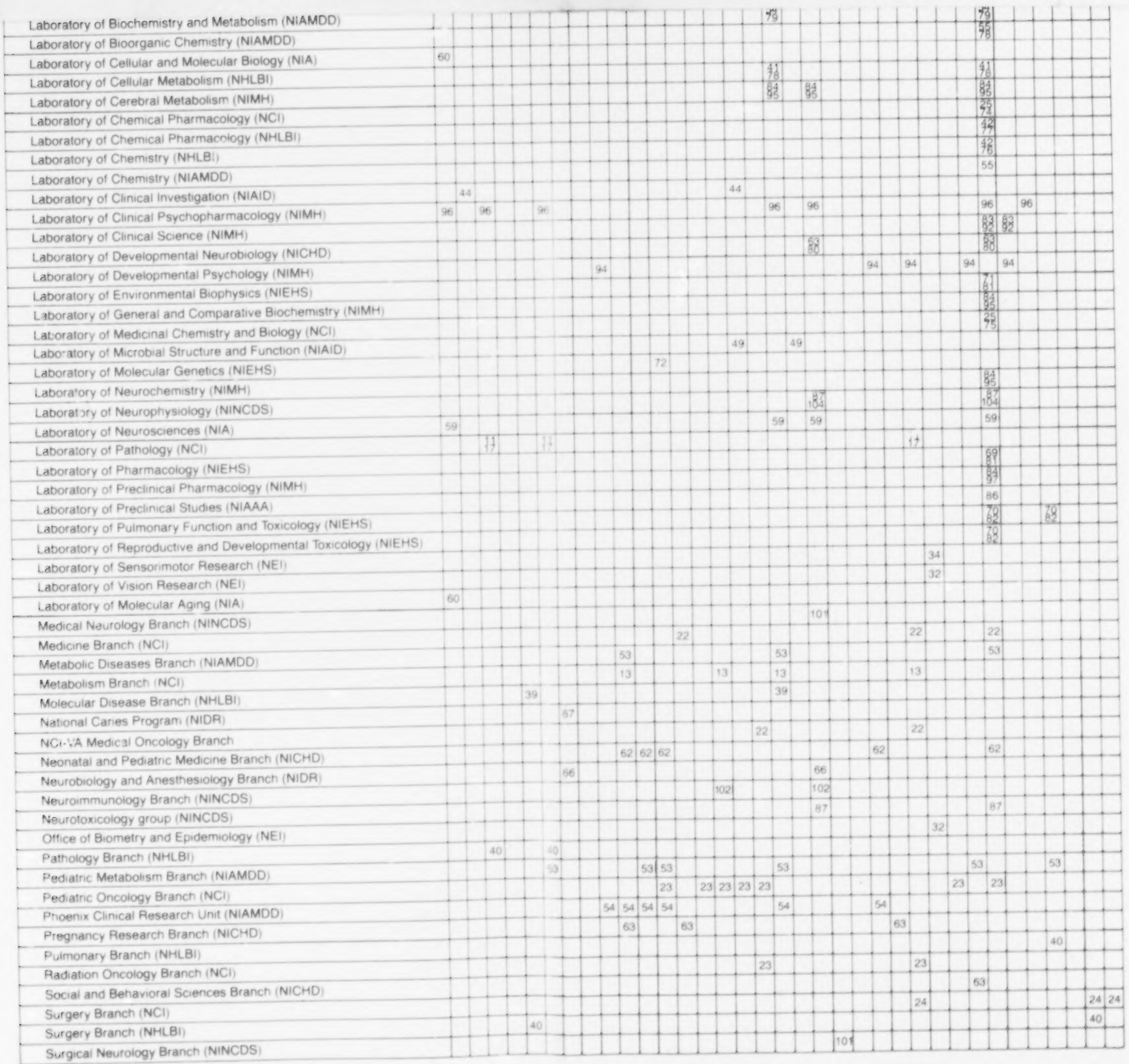
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